

# Exhibit 58

## REVIEWS

## Six Persistent Research Misconceptions

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Scientific knowledge changes rapidly, but the concepts and methods of the conduct of research change more slowly. To stimulate discussion of outmoded thinking regarding the conduct of research, I list six misconceptions about research that persist long after their flaws have become apparent. The misconceptions are: 1) There is a hierarchy of study designs; randomized trials provide the greatest validity, followed by cohort studies, with case-control studies being least reliable. 2) An essential element for valid generalization is that the study subjects constitute a representative sample of a target population. 3) If a term that denotes the product of two factors in a regression model is not statistically significant, then there is no biologic interaction between those factors. 4) When categorizing a continuous variable, a reasonable scheme for choosing category cut-points is to use percentile-defined boundaries, such as quartiles or quintiles of the distribution. 5) One should always report P values or confidence intervals that have been adjusted for multiple comparisons. 6) Significance testing is useful and important for the interpretation of data. These misconceptions have been perpetuated in journals, classrooms and textbooks. They persist because they represent intellectual shortcuts that avoid more thoughtful approaches to research problems. I hope that calling attention to these misconceptions will spark the debates needed to shelve these outmoded ideas for good.

**KEY WORDS:** study design; data interpretation; epidemiologic methods; representativeness; evaluation of interaction; multiple comparisons; percentile boundaries; statistical significance testing.

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A surprising number of misconceptions persist in the conduct of research involving human subjects. Some persist despite teachings to the contrary, and some because of teachings that should be to the contrary. To spark discussion of these issues, I list here six persistent research misconceptions, and offer a capsule summary of the problems with each of them.

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*Misconception 1. There is a hierarchy of study designs; randomized trials provide the greatest validity, followed by cohort studies, with case-control studies being least reliable.*

Randomized trials, though often considered the “gold standard” of study types, are not perfect, even in concept. Furthermore, the premise that the comparative validity of study results can be inferred from the type of study is wrong.

Although some believe that evidence from a randomized trial is as compelling as a logical proof, no empirical finding can provide absolute certainty. If randomized trials were perfect, how could they give divergent results? In fact, they are subject to various errors.<sup>1</sup> Obviously there is random error, as one would expect from a study based on random assignment. But there is also systematic error, or bias. For example, randomized trials are usually analyzed using the “intent to treat” principle, which compares the groups that are initially assigned by randomization, regardless of any subsequent non-adherence. Non-adherence results in underestimation of any treatment effect. This bias is usually considered acceptable because it is outweighed by the advantages achieved by random assignment. Underestimation of effects, however, is not acceptable in a safety trial aimed at uncovering adverse effects of the treatment. Another important source of bias in a randomized trial comes from errors in assessing the outcome, such as undercounting of outcome events. Also, even if randomization provides a balance of risk factors between groups at the start of the trial, with extended follow-up, the study groups may become progressively imbalanced through differential attrition or changes in risk factor distributions. With long-term trials, the benefits of random assignment may therefore fade with time.

In short, trials are far from perfect. Furthermore, both cohort and case-control studies will yield valid results when properly designed and carried out. Therefore, mindlessly ascribing greater validity to a study based on a hierarchy of designs<sup>2,3</sup> is fallacious. For example, the relation between cigarette smoking and lung cancer is well established, based on findings from cohort and case-control studies. The connection was never shown clearly in a randomized trial. It is not easy to assign people randomly to smoke or not smoke; however, when smoking cessation was studied as part of a multi-pronged intervention in the randomized Multiple Risk Factor Intervention Trial,<sup>4</sup> those who were

urged to cease smoking actually developed more lung cancer than those who did not receive the cessation encouragement. The results of the trial did not overthrow the findings of the many cohort and case-control studies conducted without randomization. Rather, the discrepancy was ascribed to problems with the trial.

In another high-profile example, results from large cohort studies<sup>5,6</sup> indicated that risk of coronary heart disease was reduced among postmenopausal hormone users, but later results from two randomized trials indicated either no association or an increased risk.<sup>7,8</sup> The reaction in the scientific community and the popular press<sup>9</sup> was to discredit the results from the cohort studies, presuming that they had been refuted by the randomized trials. Many continue to believe that interpretation, but in an elegant reanalysis, Hernan et al.<sup>10</sup> showed that the study populations in the cohort studies and the randomized trials were different, and that the effects of postmenopausal hormone use varied greatly according to age and time since menopause. When studies were restricted to new users of hormones, Hernan et al. showed that differences in the distribution of age and time since menopause could explain all of the apparent discrepancies. Although it is common to ascribe such discrepancies to inherent weaknesses of the nonexperimental studies, it is simplistic to assign validity based on a presumed hierarchy of study types.<sup>11</sup>

Similarly, discrepancies between cohort studies and case-control studies should not be explained away superficially by a presumed validity advantage for cohort studies over case-control studies. Properly designed case-control studies will produce the same results as properly designed cohort studies. When conflicts arise, they could stem from problems in either or both types of study. Although case-control studies have long been disparaged as being backwards versions of cohort studies, starting from disease and tracing back to possible causes, epidemiologists today understand case-control studies to be conceptually identical to cohort studies, apart from an efficiency gain that comes from sampling the denominators rather than conducting a complete census. Indeed, the efficiency gain may allow more resources for exposure assessment or case validation in case-control studies, resulting in less bias than in corresponding cohort studies of the same relation.

Those who view case-control studies as backwards versions of cohort studies sometimes make the false analogy that the controls should closely resemble the cases, except that they lack the case-defining disease. In fact, the control group in a case-control study is intended to be a sample of the population denominator that gives rise to the cases, a substitute for the full denominators obtained in a cohort study. Thus, the control group should resemble the entire study population, rather than the cases.<sup>12,13</sup> When properly designed, case-control studies can achieve the same excellent validity as properly designed cohort studies,

whereas a poorly designed trial can be unreliable. The type of study should not be taken as a guide to a study's validity.

*Misconception 2. An essential element of making valid generalizations from a study is that the study subjects constitute a representative sample of a target population.*

This misconception is tied to the view that scientific generalization involves the mechanical extrapolation of results from a sample to its source population. But that describes statistical generalization; scientific generalization is different: it is the process of constructing a correct statement about the way nature works.

Scientific generalization is the ultimate goal of scientific inquiry, but a prerequisite is designing a study that has internal validity, which is enhanced by keeping all disturbing variables constant. When have we heard of animal researchers who seek a statistically representative sample of animals? Instead, their operating principle is nearly the opposite of seeking representativeness. Thus, biologists studying mice prefer to study mice that are homogeneous with respect to genes and environment, and that differ only in respect to the experimentally manipulated variable. Unlike the statistical generalization of opinion polls or survey sampling, which merely calls for extrapolation from sample to source population, scientific generalization proceeds by informed guesses, but only from the secure platform of a valid study. Consequently, studies are stronger if they limit variability of confounding factors, as opposed to seeking representativeness. Doll and Hill<sup>14</sup> studied the mortality of male British physicians in relation to their smoking habits. Their findings were considered broadly generalizable despite the fact that their study population was unrepresentative of the general population of tobacco users with regard to sex, race, ethnicity, social class, nationality and many other variables.

When there is a legitimate question about whether an overall association varies by subgroup of some third variable, such as age or ethnic group, it may be necessary to include people drawn from a broad range of values of that third variable, but even then it is counterproductive for the study population to be representative of the source population for that variable. The goal in that case would be to include study subjects distributed evenly across the range, or in a distribution that enhances overall study efficiency. A sample that is representative of the source population will be suboptimal.<sup>15,16</sup>

*Misconception 3. If a term that denotes the product of two factors in a regression model is not statistically significant, then there is no biologic interaction between those factors.*

"Biologic" is meant here broadly, to encompass biochemical, psychological, behavioral and physical interactions. The

problem is that interaction is usually evaluated through regression models, in which the product term addresses statistical interaction rather than biologic interaction.

Biologic interaction refers to two or more causes acting in the same mechanism, with effects that are mutually dependent. It describes a state of nature. If basic effects are measured as changes in disease risk, synergistic (i.e. positive) biologic interaction is present when the joint effect of two causal factors is more than the sum of their effects acting separately.<sup>17</sup> In contrast, statistical interaction does not describe nature; it describes a mathematical model. It is typically assessed with a product term for two variables in a regression model. Its magnitude depends on the choice of measures and scale of measurement. Statistical interaction implies only that the basic functional form of a specific mathematical model is not an apt description of the relation among variables. Two factors that show biologic interaction may or may not exhibit statistical interaction, depending on the model used.

Product terms in regression models have units that can defy interpretation. If one variable is fat consumption, measured in grams per day, and another variable is pack-years of cigarettes smoked, what is the interpretation of a variable that has units of grams/day multiplied by pack-years? The challenge of interpreting such product term coefficients has fostered a focus on the p value accompanying the coefficient, rather than the magnitude of the coefficient itself. Focusing on the pvalue, or on whether the coefficient of a product term is statistically significant, only worsens the problem of mistaking statistical interaction for biologic interaction (see misconception 6). A more meaningful assessment of interaction would be to focus on the proportion of cases of a disease that one could attribute to biologic interaction.<sup>17,18</sup>

Consider a simple example from the TREAT trial (Trial to Reduce Cardiovascular Events with Aranesp Therapy),<sup>19</sup> which evaluated the risk of stroke among 4,038 patients with diabetes mellitus, chronic kidney disease, and anemia randomized to receive darbepoetin alfa or placebo. Among patients without a history of stroke, the risk of stroke during the study period was 2 % among patients receiving placebo and 4 % among patients receiving darbepoetin alfa. Among patients with a history of stroke, the corresponding risks were 4 % and 12 %. The authors noted that the risk increase was greater for darbepoetin alfa among those with a history of stroke, but they dismissed this interaction because the product term in a logistic regression model was not statistically significant. The increased risk attributable to darbepoetin alfa was 2 % in the patients without a history of stroke and 8 % among patients with a history of stroke, indicating strong biologic interaction between darbepoetin alfa and history of stroke. If the risks were merely additive, the risk would be 6 % among those with both risk factors, instead of the actual 12 %. Thus, half of the risk among those with both risk factors

appears attributable to biologic interaction, despite the authors' claim that there was no interaction.

*Misconception 4. When categorizing a continuous variable, a reasonable scheme for choosing category cut-points is to use percentile-defined boundaries, such as quartiles or quintiles of the distribution.*

There are two reasons why using percentiles is a poor method for choosing category boundaries. First, these boundaries may not correspond to the parts of the distribution where biologically meaningful changes occur. Suppose you were conducting a study of vitamin C intake and scurvy risk in the U.S. If you decided to categorize vitamin C intake by quintiles, you would find that the entire relation between vitamin C consumption and scurvy was confined to the lowest quintile, and within that category, to only a small proportion of people who were outliers in their low vitamin C intake. 10 mg/day of vitamin C can prevent scurvy, but those consuming less than that represent a fraction of 1 % of the population in the U. S.<sup>20</sup> Using percentile-based categories would make it impossible to find the effect of inadequate vitamin C intake on scurvy risk, because all intake above 10 mg/d is essentially equivalent. If we routinely use percentile cut-points, we may not know if we are facing the same problem as we would face in the study of vitamin C and scurvy. A more effective alternative would be to begin with many narrow categories, merging neighboring categories until meaningful breaks in risk become evident.

The second problem with percentile-based categories is the difficulty in comparing results across studies, because categories across studies using percentile category boundaries are unlikely to correspond. This problem can be averted by expressing boundary points in terms of the natural units of the variable (such as mg/d for vitamin C intake). It is also useful to report within-category means or medians.

*Misconception 5. One should always report P values or confidence intervals that have been adjusted for multiple comparisons.*

Traditional adjustments for multiple comparisons involve inflating the P value or the width of a confidence interval according to the number of comparisons conducted. If one is analyzing biological data that are replete with actual associations, the premise for traditional adjustments is shaky and the adjustments are difficult to defend. The concern for multiple comparisons stems from fear of finding falsely significant findings (type I errors in the lingo of statistics). In misconception 6, we discuss the problems with using statistical significance testing for data analysis in the first place. But before considering those problems, let us consider the rationale for adjusting reported results for multiple comparisons.

Despite the fact that a single significance test is intended to have a 5 % probability (at the conventionally used level) of being significant when the null hypothesis is true, and



therefore multiple tests when properly carried out should each have this property, there is a concern that when making multiple tests, the probability of a spurious result is increased. Of course, as the number of tests increases, the probability that one or more of them would be falsely positive increases, but that is only because many tests are being conducted. Adjustments for multiple comparisons will reduce these type I errors, but they do so at the expense of increasing type II errors, which are nonsignificant test results in the presence of a real association. When observed associations are all the result of chance, type I errors can occur, but type II errors cannot occur. Conversely, when the observed associations all reflect actual relationships, type II errors can occur, but type I errors cannot. Thus, the context of any analysis has fundamental implications regarding the interpretation of the data. In particular, it is absurd to make adjustments that reduce type I errors at the expense of increasing type II errors without some evaluation of the estimated relative cost and frequency of each type of error.

If scientists were put to work studying random numbers instead of biologic data, all the significant results they reported would represent type I errors, and adjustments for multiple comparisons would make sense; some skeptics believe that studies of genome-wide association scans may approximate this situation.<sup>21</sup> But when scientists are studying biological relations rather than random numbers, the premise that type I errors are the major concern may be wrong.<sup>22</sup> A more rigorous evaluation of the need for multiplicity adjustments would begin with an assessment of the tenability of the thesis that the data are essentially random numbers. If one is studying experiments on psychic phenomena, skepticism about the results might lend support to multiplicity adjustments. If one is studying physiologic effects of pharmaceutical agents, real associations are to be expected and the adjustments are more difficult to defend. Studying single nucleotide polymorphisms in relation to a given disease might be a middle ground. One approach to this issue that is theoretically more defensible is a Bayesian approach, which assigns prior credibility to various levels of association and adjusts by using Bayes' theorem to calculate posterior credibility.<sup>23,24</sup>

*Misconception 6. Significance testing is useful and important for the interpretation of data.*

Significance testing has led to far more misunderstanding and misinterpretation than clarity in interpreting study results.<sup>25–28</sup> A significance test is a degraded version of the P value, a statistic that blends precision with effect size, thus confusing two essential aspects of data interpretation. Measuring effect size and its precision as separate tasks is a more direct and clearer approach to data interpretation.

For research studies that aim to measure associations, and infer whether they reflect causal connections, focusing on the magnitude of these associations ought to be the primary

goal: estimation of effects is decidedly preferable to statistical testing. Ideally, a study estimates the magnitude of the effect size, and analyzes the possible errors that might have distorted it. Systematic errors such as confounding from measured factors can be dealt with through analytic methods; other systematic errors, such as the effects of measurement error or selection bias, can be addressed through sensitivity analyses (also known as bias analysis). Random error is typically expressed through confidence intervals, giving a range of parameter values that are consistent with the data to a specified level.

It is unfortunate that a confidence interval, from which both an estimate of effect size and its measurement precision can be drawn, is typically used merely to judge whether it contains the null value or not, thus converting it to a significance test. Significance tests are a poor classification scheme for study results; strong effects may be incorrectly interpreted as null findings because authors fallaciously interpret lack of statistical significance to imply lack of effect, or weak effects may be incorrectly interpreted as important because they are statistically significant. Rather than be used as surrogate significance tests, confidence intervals ought to be interpreted as quantitative measures indicating magnitude of effect size and degree of precision, with little attention paid to the precise location of the boundaries of the confidence interval. This advice is backed by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, but nevertheless often overlooked even by reviewers and editors whose journals support the requirements.<sup>29</sup>

Many misconceptions derive from reliance on statistical significance testing. The focus on the statistical significance of interaction terms instead of measuring interaction, as discussed above, is one example. The evaluation of dose–response trends simply by declaring that there is or is not a significant trend, rather than expressing the magnitude and ideally the shape of that trend, is another. Yet another is the advice sometimes offered to calculate the power of a study when reporting results, especially if those results are not statistically significant. Reporting the power of a study as part of the results is called “post-hoc” power calculation.<sup>30</sup> Power calculations are based on a hypothesis about the level of association that is to be distinguished from a null association, but when the study results are on hand, there is no longer any need to hypothesize about the magnitude of the association, because you now have an estimate of it. A confidence interval for the estimated association conveys all the relevant information; nothing further is to be gained from a power calculation.

The unfortunate consequence of the focus on statistical significance testing has been to foster a dichotomous view of relationships that are better assessed in quantitative terms. This distinction is more than a nicety. Every day there are important, regrettable and avoidable misinterpretations of data that results from the confusing fog of

statistical significance testing. Most of these errors could be avoided if the focus were shifted from statistical testing to estimation.

## CONCLUSION

Why do such important misconceptions about research persist? To a large extent these misconceptions represent substitutes for more thoughtful and difficult tasks. It is simpler to resolve a discrepancy between a trial and a nonexperimental study in favor of the trial, without undertaking the laborious analysis that Hernán et al. did.<sup>10</sup> It is easy to declare that a result is not statistically significant, falsely implying that there is no indication of an association, rather than to consider quantitatively the range of associations that the data actually support. These misconceptions involve taking the low road, but when that road is crowded with others taking the same path, there may be little reason to question the route. Indeed, these misconceptions are often perpetuated in journals, classrooms and textbooks. I believe that the best prospect for improvement is to raise consciousness about the issues, with reasoned debate. Max Planck once said, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”<sup>31</sup> To the extent that this cynical view is correct, we can expect to see outmoded concepts fade away slowly at best. I hope that calling attention to these misconceptions will spark the needed debates and be a catalyst for change.

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**Conflict of Interest:** The author declares no conflict of interest.

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# Exhibit 59

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4 FOR THE DISTRICT OF NEW JERSEY

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9 IN RE: JOHNSON & JOHNSON TALCUM )

10 POWDER PRODUCTS MARKETING, SALES )

11 PRACTICES, AND PRODUCTS LIABILITY ) MDL No. 2738 (FLW)(LHG)

12 LITIGATION )

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17 VIDEOTAPED DEPOSITION OF ANNE MCTIERNAN, PH.D.

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<p>1 APPEARANCES (CONTINUED)</p> <p>2</p> <p>3 For Imerys:</p> <p>4 Nancy M. Erfle, Esquire</p> <p>5 Gordon &amp; Rees Scully Mansukhani, LLP</p> <p>6 121 SW Morrison Street</p> <p>7 Suite 1575</p> <p>8 Portland, OR 97204</p> <p>9 503.222.1075</p> <p>10 503.616.3600 Fax</p> <p>11 Nerfle@grsm.com</p> <p>12 For PTI Union, LLC and PTI Royston:</p> <p>13 Michael Anderton, Esquire</p> <p>14 Tucker Ellis LLP</p> <p>15 950 Main Avenue</p> <p>16 Suite 1100</p> <p>17 Cleveland, Ohio 44113-7213</p> <p>18 216.696.4835</p> <p>19 216.592.5009 Fax</p> <p>20 Michael.anderton@tuckerellis.com</p> <p>21 For Personal Care Products Council:</p> <p>22 Thomas T. Locke, Esquire</p> <p>23 Seyfarth Shaw LLP</p> <p>24 975 F Street NW</p> <p>25 Washington, D.C. 20004-1454</p> <p>202.828.5376</p> <p>202.641.9276 Fax</p> <p>Tlocke@seyfarth.com</p> <p>Also present: Anthony Bocci, Videographer</p>	<p>1 EXHIBIT INDEX (CONTINUED)</p> <p>2</p> <p>3 Exhibit No. 6 World Cancer Research Fund International, CUP panel web page excerpt, "CUP expert panel." 83</p> <p>4</p> <p>5 Exhibit No. 7 World Cancer Research Fund web page excerpt, "Myths and controversies about what causes cancer." 98</p> <p>6</p> <p>7</p> <p>8 Exhibit No. 8 American Institute for Cancer Research, "GMOs and other hot topics." 103</p> <p>9</p> <p>10 Exhibit No. 9 Hutch News, "How to reduce the odds of getting cancer." 105</p> <p>11 Exhibit No. 10 World Cancer Research Fund and American Institute for Cancer Research, "Judging the evidence." 110</p> <p>12</p> <p>13</p> <p>14 Exhibit No. 11 "Language from CUP judging the evidence report quoted without citation in Dr. McTiernan's expert report." 138</p> <p>15</p> <p>16</p> <p>17 Exhibit No. 12 Article, "Information bias in epidemiological studies with a special focus on obstetrics and gynecology." 164</p> <p>18</p> <p>19 Exhibit No. 13 Article, "Prospective study of talc use and ovarian cancer." 167</p> <p>20</p> <p>21 Exhibit No. 14 Article, "Genital talc exposure and risk of ovarian cancer." 169</p> <p>22</p> <p>23 Exhibit No. 15 Article, "Perineal talc use and ovarian cancer." 180</p> <p>24</p> <p>25</p>

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<p>1 EXHIBIT INDEX (CONTINUED)</p> <p>2</p> <p>3 Exhibit No. 16 Article, "Genital use of talc 192 and risk of ovarian cancer: A meta-analysis."</p> <p>4 Exhibit No. 16A Article, "Genital use of talc 197 and risk of ovarian cancer: A meta-analysis."</p> <p>5 Exhibit No. 17 Study, "Systematic review and 203 meta-analysis of the association between perineal use of talc and risk of ovarian cancer."</p> <p>6</p> <p>7 Exhibit No. 18 Article, "The relationship 232 between perineal cosmetic talc usage and ovarian talc particle burden"</p> <p>8 Exhibit No. 19 Collection of tests from 260 John Hopkins' deposition, his Exhibit No. 24.</p> <p>9 Exhibit No. 20 Collection of tests from 263 John Hopkins' deposition, his Exhibit No. D-1, including "The whole story."</p> <p>10</p> <p>11 Exhibit No. 21 "IARC monographs on the 274 evaluation of carcinogenic risks to humans. Volume 93 - Carbon black, titanium dioxide, and talc," Lyon, France, 2010.</p> <p>12 Exhibit No. 22 Article, "Perineal use of 279 talc and risk of ovarian cancer."</p> <p>13 Exhibit No. 23 Testing document from 302 Ms. Pier's deposition, Pier Exhibit No. 47.</p> <p>14 Exhibit No. 24 Copies of Dr. McTiernan's 303 invoices to Ms. Parfitt.</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>1 BE IT REMEMBERED that on Monday,</p> <p>2 January 28, 2019, at 1301 Second Avenue, Suite 2000,</p> <p>3 Seattle, Washington, at 9:11 a.m., before Terilynn</p> <p>4 Simons, Certified Court Reporter, CCR, RMR, CRR, CLR,</p> <p>5 appeared ANNE MCTIERNAN, PH.D., the witness herein;</p> <p>6 WHEREUPON, the following proceedings</p> <p>7 were had, to wit:</p> <p>8</p> <p>9 &lt;&lt;&lt;&lt;&lt;&lt; &gt;&gt;&gt;&gt;&gt;&gt;</p> <p>10</p> <p>11 VIDEOGRAPHER: We are now on the</p> <p>12 record. My name is Anthony Bocci. I am a videographer</p> <p>13 for Golkow Litigation Services. Today's date is</p> <p>14 1/28/2019, and the time is 9:11 a.m.</p> <p>15 This video deposition is being held at 1301 Second</p> <p>16 Avenue, Suite 2000, Seattle, Washington 98101 in the</p> <p>17 matter of In Re Johnson &amp; Johnson Talcum Powder Products</p> <p>18 Marketing Sales Practices and Products Liability</p> <p>19 Litigation, for the United States District Court,</p> <p>20 District of New Jersey.</p> <p>21 The deponent is Dr. Anne McTiernan.</p> <p>22 Will Counsel please identify themselves for the</p> <p>23 record.</p> <p>24 MS. PARFITT: Good morning. Michelle</p> <p>25 Parfitt, counsel for the plaintiffs.</p>
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<p>1 EXHIBIT INDEX (CONTINUED)</p> <p>2</p> <p>3 Exhibit No. 25 Rule 26 expert report of Anne 304 McTiernan, MD, PHD, dated November 16, 2018.</p> <p>4</p> <p>5 Exhibit No. 26 "Draft screening assessment," 306 dated December 2018.</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p>1 MS. GARBER: Good morning. Cynthia</p> <p>2 Garber on behalf of the plaintiffs.</p> <p>3 MR. GOLOMB: Richard Golomb on behalf</p> <p>4 of Plaintiffs.</p> <p>5 MS. ERFLE: Nancy Erfle on behalf of</p> <p>6 Imerys Talc America.</p> <p>7 MR. LOCKE: Tom Locke from Personal</p> <p>8 Care Products Council.</p> <p>9 MR. ANDERTON: Michael Anderton for</p> <p>10 PTI Royston, LLC and PTI Union, LLC.</p> <p>11 MR. HALPERIN: Benjamin Halperin for</p> <p>12 Johnson &amp; Johnson.</p> <p>13 MS. GUTIERREZ: Susan Gutierrez for</p> <p>14 Johnson &amp; Johnson.</p> <p>15 MR. WILLIAMS: And Bart Williams for</p> <p>16 Johnson &amp; Johnson.</p> <p>17 VIDEOGRAPHER: Thank you.</p> <p>18 Will the court reporter now please swear in the</p> <p>19 witness.</p> <p>20</p> <p>21 ANNE MCTIERNAN, PH.D., having been first duly sworn</p> <p>22 by the Certified Court Reporter,</p> <p>23 testified as follows:</p> <p>24 /////</p> <p>25 /////</p>

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<p>1 EXAMINATION</p> <p>2 BY MR. WILLIAMS:</p> <p>3 Q Good morning, Dr. McTiernan.</p> <p>4 A Good morning.</p> <p>5 Q We just met this morning. My name is Bart Williams, and</p> <p>6 I represent Johnson &amp; Johnson in this matter, which is</p> <p>7 pending in the District of New Jersey Federal Court.</p> <p>8 Are you aware of that?</p> <p>9 A Yes.</p> <p>10 Q Have you ever had your deposition taken before?</p> <p>11 A Never.</p> <p>12 Q The way this will work is I'll ask you questions.</p> <p>13 Counsel may interpose objections to my questions. There</p> <p>14 will be no judge here ruling on the objections, and after</p> <p>15 the objections, if any, you are supposed to answer the</p> <p>16 question.</p> <p>17 Do you understand that?</p> <p>18 A Yes.</p> <p>19 Q My understanding is that you have provided us with a USB</p> <p>20 drive; is that correct?</p> <p>21 A Michelle Parfitt provided you with that drive, yes.</p> <p>22 Q Are you aware of what's on that drive?</p> <p>23 A Yes. It's all the documents that I've used in forming my</p> <p>24 opinion.</p> <p>25 Q Are all of the files on the USB drive documents that you</p>	<p>1 MS. PARFITT: If I may, I am not sure</p> <p>2 that Dr. McTiernan knows that.</p> <p>3 The additional materials, they are not, to my</p> <p>4 knowledge, on that thumb drive.</p> <p>5 It was a list of some additional materials. I'm not</p> <p>6 sure that she's reviewed them all, and please feel free</p> <p>7 to make that inquiry, if you will, but I don't believe,</p> <p>8 Mr. Williams, they may be included on that thumb drive.</p> <p>9 That thumb drive should include the report, the</p> <p>10 references to the report.</p> <p>11 MR. WILLIAMS: Okay.</p> <p>12 Q (By Mr. Williams) Dr. McTiernan, when were you first</p> <p>13 approached about any involvement in talcum powder</p> <p>14 litigation?</p> <p>15 A It should have been 2016.</p> <p>16 Q And by whom were you approached?</p> <p>17 A By Ms. Parfitt.</p> <p>18 Q Michelle Parfitt, counsel who is--</p> <p>19 A Yes.</p> <p>20 Q One thing I should have told you, in order for the court</p> <p>21 reporter to take down everything that is said, you need</p> <p>22 to wait until I'm completely finished--</p> <p>23 A Oh, sorry.</p> <p>24 Q --with my question.</p> <p>25 You should take a pause and then answer the</p>
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<p>1 considered in connection with your opinions in this case?</p> <p>2 A Yes.</p> <p>3 Q Are there any other files on the USB drive?</p> <p>4 A Not to my knowledge there are no other files.</p> <p>5 Q Can you be a little bit more particular about what types</p> <p>6 of documents, categories of documents, are contained on</p> <p>7 the drive?</p> <p>8 A So these will be scientific manuscripts published in</p> <p>9 peer-reviewed journals.</p> <p>10 They will be some expert testimony.</p> <p>11 There was government reports, and I don't have the</p> <p>12 full list right in front of me, so there are hundreds of</p> <p>13 these things, but in general classifications, I think</p> <p>14 that is-- that covers it generally.</p> <p>15 Q Those are all the things you recall at this time?</p> <p>16 A That's what I recall.</p> <p>17 My report should be on there as well, my CV, and</p> <p>18 government reports of-- other expert reports-- if I</p> <p>19 mentioned that.</p> <p>20 Q Let me stop you there.</p> <p>21 A Yeah.</p> <p>22 Q Does the USB drive contain all of the materials that were</p> <p>23 just recently produced to the defense in the case a few</p> <p>24 days ago, which were entitled, "Additional materials"</p> <p>25 that you had reviewed?</p>	<p>1 question, okay?</p> <p>2 A Mm-hm, okay.</p> <p>3 Q Otherwise, she has to cut off part of the question, write</p> <p>4 down your partial answer, and then the rest of my</p> <p>5 question.</p> <p>6 Do you understand that?</p> <p>7 A Okay, yes.</p> <p>8 Q So the first person who approached you was Michelle</p> <p>9 Parfitt?</p> <p>10 A Yes.</p> <p>11 Q Do you remember--</p> <p>12 A For this-- yes, for this litigation, yes.</p> <p>13 Q When in 2016 did Ms. Parfitt approach you?</p> <p>14 A I don't have that in my head.</p> <p>15 We should have a record of that first interaction.</p> <p>16 Q I will just get your memory for now.</p> <p>17 Was it winter, spring, summer or fall?</p> <p>18 A It would be late summer.</p> <p>19 Q Did Ms. Parfitt contact you at your place of business?</p> <p>20 A She approached me first by an e-mail at my institutional</p> <p>21 e-mail address, yes.</p> <p>22 Q And what is that e-mail address?</p> <p>23 A At that time it was probably still amctiern@fhcrc.</p> <p>24 My institution has changed the middle part to</p> <p>25 FredHutch, so I believe she did the first one.</p>

<p style="text-align: right;">Page 14</p> <p>1 Either one goes to the same place.</p> <p>2 Q Have you known Ms. Parfitt or any of the other</p> <p>3 plaintiffs' lawyers prior to their contacting you?</p> <p>4 A No, I did not.</p> <p>5 Q How long after Ms. Parfitt first contacted you did you</p> <p>6 agree to work with them in connection with the talcum</p> <p>7 powder litigation?</p> <p>8 A It was approximately two months, and my institution</p> <p>9 requires that I get permission for doing such consulting,</p> <p>10 so the process took approximately two months before I</p> <p>11 received approval.</p> <p>12 Q As of late summer 2016, when Ms. Parfitt first contacted</p> <p>13 you, what institution are you talking about?</p> <p>14 A Oh, so Fred Hutch Cancer Research Center in Seattle.</p> <p>15 Q And if it took two months, that would mean that it was</p> <p>16 late summer, early fall when you had received approval;</p> <p>17 is that correct?</p> <p>18 A I believe, yes.</p> <p>19 Q And that's late summer, early fall of 2016, right?</p> <p>20 A I believe, yes.</p> <p>21 Q How much per hour are you billing for the literature</p> <p>22 review and preparation for your report in this matter?</p> <p>23 A That was \$450 an hour.</p> <p>24 Q At what rate are you charging for your time spent</p> <p>25 providing deposition testimony?</p>	<p style="text-align: right;">Page 16</p> <p>1 A Yes.</p> <p>2 Q When did you first see this?</p> <p>3 A Approximately a month ago.</p> <p>4 Q In response to this deposition notice, which lists</p> <p>5 certain categories of documents, have you brought any</p> <p>6 documents with you here today?</p> <p>7 A We have documents for reports that were available only</p> <p>8 recently, so too recent to have them on the thumb drive,</p> <p>9 so these include the Health Canada report, weight of</p> <p>10 evidence, the screening-- the draft screening assessment,</p> <p>11 risk management scope, information sheet, key messages,</p> <p>12 and a "Draft systematic review of meta-analysis" by</p> <p>13 Taher, so it's a signed manuscript.</p> <p>14 Q Anything else?</p> <p>15 A These others are all in my list of documents. These are</p> <p>16 just copies of them.</p> <p>17 Q So just let me clear that up.</p> <p>18 You have just mentioned that there are some reports</p> <p>19 in--</p> <p>20 A The Health Canada report.</p> <p>21 Q Let me just take them one at a time.</p> <p>22 A I'm sorry.</p> <p>23 Q You listed the Health Canada report, correct?</p> <p>24 A Yes.</p> <p>25 Q Something called the draft screening assessment?</p>
<p style="text-align: right;">Page 15</p> <p>1 A \$650.</p> <p>2 Q Is that the same amount that you would charge for hearing</p> <p>3 testimony if you were to testify at the Daubert, and</p> <p>4 that's D-A-U-B-E-R-T, hearing in the summer of 2019?</p> <p>5 A Yes.</p> <p>6 Q Do you charge for travel related to your work as an</p> <p>7 expert witness, separate and apart from any work that you</p> <p>8 may do while traveling?</p> <p>9 A I have not previously been an expert witness, so I can't</p> <p>10 give you an answer on what I usually do.</p> <p>11 Q So this is the very first time in your career where you</p> <p>12 have served as an expert witness; is that correct?</p> <p>13 A That's right.</p> <p>14 (Exhibit No. 1 marked</p> <p>15 for identification.)</p> <p>16</p> <p>17 Q (By Mr. Williams) We have marked as Deposition Exhibit</p> <p>18 No. 1 the deposition notice, and we will hand that out to</p> <p>19 you through your counsel.</p> <p>20 MS. PARFITT: I believe you have that,</p> <p>21 Anthony, the first notice.</p> <p>22 Q (By Mr. Williams) Do you have Exhibit No. 1, the</p> <p>23 deposition notice, in front of you?</p> <p>24 A Yes.</p> <p>25 Q Is this something you have seen before?</p>	<p style="text-align: right;">Page 17</p> <p>1 A So these are all part of the Health Canada report.</p> <p>2 These are the components of it.</p> <p>3 A screening assessment document, weight of evidence</p> <p>4 document, a document called "Risk management scope," one</p> <p>5 called-- the title is, "Talc - potential risk of lung</p> <p>6 effects and ovarian cancer." I am calling it key</p> <p>7 messages because that's the first title underneath that.</p> <p>8 There's a talc information sheet.</p> <p>9 And a government of Canada talc sheet.</p> <p>10 It looks like it's a public messages sheet.</p> <p>11 The last thing is a systematic review of</p> <p>12 meta-analysis of the association between perineal use of</p> <p>13 talc and risk of ovarian cancer by Taher, et al.</p> <p>14 Q And let me ask you to go a little bit more slowly when</p> <p>15 you read today so that the court reporter can get it</p> <p>16 down.</p> <p>17 Is that okay with you?</p> <p>18 A Yes.</p> <p>19 Q Is it accurate to say that the items you have just listed</p> <p>20 were not in your possession at the time that you prepared</p> <p>21 your report that has been provided in this case?</p> <p>22 A That is correct.</p> <p>23 They were published after that period.</p> <p>24 Q Is it accurate to say that none of the materials that you</p> <p>25 have in front of you now were able to inform the opinions</p>

<p style="text-align: right;">Page 18</p> <p>1 that you expressed in the report, which predated your</p> <p>2 receipt of those materials?</p> <p>3 A The Health Canada report, that is true for.</p> <p>4 However, the other documents that I have here, one</p> <p>5 is a paper that I cited from Blount.</p> <p>6 One is information from the FDA website, which is--</p> <p>7 I was able to access before doing my report.</p> <p>8 Then the last thing is-- I'm sorry, it's a</p> <p>9 deposition of Dr. Blount held last April, so I had access</p> <p>10 to that earlier as well.</p> <p>11 Q Let's do this, we previously went through a list of</p> <p>12 materials, most of which related to the Health Canada</p> <p>13 report.</p> <p>14 Do you remember that?</p> <p>15 A Yes.</p> <p>16 Q Other than that set of materials that you previously</p> <p>17 described, is everything in the blue folder that's in</p> <p>18 front of you, that you have brought with you today, a</p> <p>19 duplicate of another report that has already been</p> <p>20 produced to us?</p> <p>21 A Yes.</p> <p>22 There was also one list here of additional</p> <p>23 materials, so that should have been-- additional</p> <p>24 materials to Dr. McTiernan, and that should be in your</p> <p>25 list of what you have as well.</p>	<p style="text-align: right;">Page 20</p> <p>1 Q We will take a look at that during a break and perhaps</p> <p>2 get a copy of it.</p> <p>3 A Okay.</p> <p>4 Q When were the notes that you have written on your expert</p> <p>5 report written on the report?</p> <p>6 A In the past week.</p> <p>7 I realized, as I was reviewing and preparing, that I</p> <p>8 had not used a program that would give the full name of</p> <p>9 the references, so to aid in my review, I wrote in the</p> <p>10 first author of the documents, the manuscripts that I was</p> <p>11 referring to.</p> <p>12 Everything listed here is-- that I've written is the</p> <p>13 first author of an article, and then I've also underlined</p> <p>14 a few places to jog my memory.</p> <p>15 Q Other than what you've just described, are there any</p> <p>16 other notations that appear on the report document?</p> <p>17 A No, not to my knowledge, no.</p> <p>18 Q Did you bring with you today any invoices reflecting</p> <p>19 statements that you have given to plaintiffs' counsel for</p> <p>20 payment?</p> <p>21 A I did not bring them myself, but I believe you have them.</p> <p>22 MS. PARFITT: We did-- we have them.</p> <p>23 If we can just take a look at them-- they were just</p> <p>24 sent this morning to us, to my office, so if I could have</p> <p>25 a chance to look through them, and maybe after the break</p>
<p style="text-align: right;">Page 19</p> <p>1 Q We are going to mark a copy of that additional materials</p> <p>2 list in a moment, but for now, is it accurate that at the</p> <p>3 time that you prepared your report in this case, which</p> <p>4 was submitted to us in November of 2018, you had not</p> <p>5 reviewed the additional materials list materials that you</p> <p>6 have just pointed to?</p> <p>7 A That is correct.</p> <p>8 Those were not available at that time.</p> <p>9 Q Let's mark as Exhibit No. 2 to the deposition a copy of</p> <p>10 your expert report from November of 2018.</p> <p>11 I think your counsel already has that.</p> <p>12 (Exhibit No. 2 marked</p> <p>13 for identification.)</p> <p>14</p> <p>15 Q (By Mr. Williams) Is the document marked Exhibit No. 2 a</p> <p>16 copy of the expert report that you prepared in this case?</p> <p>17 A Yes, it is.</p> <p>18 Q It's dated November 16th, 2018?</p> <p>19 A Yes.</p> <p>20 Q You have a copy of that report in front of you that you</p> <p>21 are holding right now; is that right?</p> <p>22 A Yes.</p> <p>23 Q Does the copy that you are holding right now have notes</p> <p>24 on it?</p> <p>25 A Yes, it does.</p>	<p style="text-align: right;">Page 21</p> <p>1 we can get them marked.</p> <p>2 Would that be appropriate?</p> <p>3 MR. WILLIAMS: That's fine.</p> <p>4 MS. PARFITT: The only other thing I</p> <p>5 ask, Mr. Williams, could we perhaps note the Exhibit 1A,</p> <p>6 the objection to the notice of depo?</p> <p>7 MR. WILLIAMS: Sure.</p> <p>8 MS. PARFITT: Thank you.</p> <p>9 (Exhibit No. 1A marked</p> <p>10 for identification.)</p> <p>11</p> <p>12 Q (By Mr. Williams) Your counsel-- we have premarked as</p> <p>13 Exhibit No. 1A the objections that were served by</p> <p>14 Plaintiffs' counsel to the deposition notice that we</p> <p>15 provided.</p> <p>16 Have you seen that before?</p> <p>17 It's in front of you now.</p> <p>18 A This, no, I have not.</p> <p>19 Q So you have never seen the objections?</p> <p>20 A No, I have not.</p> <p>21 Q Did counsel consult with you at all at the time that was</p> <p>22 prepared?</p> <p>23 A No.</p> <p>24 Q Let's go back to the point in time when you first spoke</p> <p>25 with plaintiffs' counsel.</p>



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<p>1 You said Ms. Parfitt reached out to you by e-mail at</p> <p>2 your institution, which was the Fred Hutch Institution;</p> <p>3 is that right?</p> <p>4 A Yes.</p> <p>5 Q Was anyone else on the phone?</p> <p>6 A No.</p> <p>7 Q How long was that call?</p> <p>8 A I don't remember.</p> <p>9 I think it was brief, but I don't remember.</p> <p>10 Q And you said "I think" that it took a few months for the</p> <p>11 process at your institution to be completed; is that</p> <p>12 right?</p> <p>13 A Yes.</p> <p>14 Q How long after that first approach by Ms. Parfitt in the</p> <p>15 summer, late summer, of 2016 did you decide that you</p> <p>16 would in fact want to serve as an expert in this matter?</p> <p>17 A I decided within a week that I would be interested, but I</p> <p>18 am required to do this process at my institution which</p> <p>19 involves informing my division director and the senior</p> <p>20 vice presidents of the institution as well as the</p> <p>21 president, and in aiding that, our legal counsel reviews</p> <p>22 all of these requests to do such consulting.</p> <p>23 So that process happened to take a while.</p> <p>24 This time, I'm not sure. I think somebody was on</p> <p>25 vacation, so that's why it took two months, so during--</p>	<p>1 Q When you say you did preliminary searches on Medline, can</p> <p>2 you recall any articles that you came up with?</p> <p>3 A I previously had already reviewed for the New York</p> <p>4 Times-- when they contacted me about my scientific</p> <p>5 opinion or my clinical opinion of this matter, I had been</p> <p>6 given two of the cohort study papers, one by Gertig, et</p> <p>7 al., and one by Houghton, et al., and so I briefly</p> <p>8 reviewed those, and-- as well as the Terry case-control</p> <p>9 study in order to talk with the New York Times, so I knew</p> <p>10 about those papers.</p> <p>11 In the epidemiology field, we often see things over</p> <p>12 time.</p> <p>13 This has been something that has been studied for</p> <p>14 quite a few years, so I've been aware of the issue but</p> <p>15 have not done a systematic review and not done a causal</p> <p>16 analysis, was not a focus of my research at that point.</p> <p>17 Q At the time that you agreed to participate as an expert</p> <p>18 in this litigation, is it accurate to say that the</p> <p>19 studies that you had reviewed included the Terry 2013</p> <p>20 analysis, the Gertig cohort study, the Houghton cohort</p> <p>21 study, you had reviewed as all those things before you</p> <p>22 decided to participate; is that true?</p> <p>23 A I had read those, yes.</p> <p>24 Q And you can't remember anything else, as you sit here</p> <p>25 right now, that you had reviewed before you made that</p>
Page 23	Page 25
<p>1 in order to start the process, I had to be interested in</p> <p>2 doing this, so that's why I did it, but I couldn't firmly</p> <p>3 say I could do it until they gave me approval.</p> <p>4 Q In that week's period of time, between the time</p> <p>5 Ms. Parfitt first contacted you and the time that you</p> <p>6 made the decision to participate in this litigation as an</p> <p>7 expert, what, if any, documents relating to talcum powder</p> <p>8 and ovarian cancer did you review?</p> <p>9 A I had already known some of the literature, some of the--</p> <p>10 for example, the pooled analysis by Terry, et al., I had</p> <p>11 already reviewed that in the past, and I think I did some</p> <p>12 preliminary searches through Medline to see what the</p> <p>13 available data were, but I did not do a systematic</p> <p>14 review.</p> <p>15 I was not able to share that with the counsel, who</p> <p>16 was Ms. Parfitt at this point, because I wasn't able to</p> <p>17 officially consult, but I was curious. I wanted to know</p> <p>18 what the data was looking like, what papers were</p> <p>19 available.</p> <p>20 Q Other than the Terry 2013 article that you mentioned and</p> <p>21 some preliminary searches that you did on Medline, is</p> <p>22 there anything else you did in that week's period of</p> <p>23 time?</p> <p>24 A In that week? I don't recall anything else in that</p> <p>25 period.</p>	<p>1 decision?</p> <p>2 A I can't remember others.</p> <p>3 Q Were there others or not?</p> <p>4 A I can't remember.</p> <p>5 I believe that I only looked at those two cohort</p> <p>6 studies and the Terry pooled analysis.</p> <p>7 Q Let me ask you to focus on Exhibit No. 2, your report.</p> <p>8 Do you have that in front of you?</p> <p>9 A Yes.</p> <p>10 Q Does that report contain all of the opinions that you</p> <p>11 intend to offer at any hearing on this matter?</p> <p>12 A Yes, unless-- so you are talking about any future-- any</p> <p>13 future questioning I face in the court?</p> <p>14 If there's more research that is published by that</p> <p>15 time, I would want to know about it to see if it affects</p> <p>16 my opinion or what the research is.</p> <p>17 As a scientist I would want to keep up to date, but</p> <p>18 for right now, this is my scientific opinion, what's in</p> <p>19 this report.</p> <p>20 Q Today is my opportunity to ask you questions about your</p> <p>21 opinions in this matter.</p> <p>22 You understand that, right?</p> <p>23 A Yes.</p> <p>24 Q Have you modified your opinions in this litigation beyond</p> <p>25 the opinions set forth in Exhibit No. 2?</p>

<p style="text-align: right;">Page 26</p> <p>1 A No, I have not.</p> <p>2 Q Are there any few or additional opinions that you expect</p> <p>3 to testify to at any hearing in this matter, other than</p> <p>4 what is contained in your report, Exhibit No. 2?</p> <p>5 A Nothing that I foresee, that I expect.</p> <p>6 Q Did you personally type the report that's marked as</p> <p>7 Exhibit No. 2?</p> <p>8 A Yes, I did.</p> <p>9 Q Did anyone assist you in the preparation of your report?</p> <p>10 A The only assistance I had was occasionally if I couldn't</p> <p>11 get a paper myself, through my own institutional library,</p> <p>12 then we have an administrative assistant that I can ask</p> <p>13 for that, and I believe I asked for a couple of papers</p> <p>14 through that source.</p> <p>15 There were a couple of times when I asked</p> <p>16 Ms. Parfitt's firm if they had a paper. This was quite a</p> <p>17 few months after that period, perhaps half a year or</p> <p>18 longer by the time I asked them.</p> <p>19 Q When did you start drafting the litigation report marked</p> <p>20 as Exhibit No. 2?</p> <p>21 A That would have been winter of 2016 to spring of 2017.</p> <p>22 Q Since you typed the report yourself, am I right that you</p> <p>23 have a file of it either at home or on your office</p> <p>24 computer?</p> <p>25 A Yes, on my home computer.</p>	<p style="text-align: right;">Page 28</p> <p>1 was given approval to work on this, so anything I read</p> <p>2 before that, I did not charge my time.</p> <p>3 Q (By Mr. Williams) Is it accurate to say that the 240</p> <p>4 hours reflects all of the hours, through today, that you</p> <p>5 have spent on this matter?</p> <p>6 A Yes.</p> <p>7 Q And you broke it down to 211 hours through December 2018</p> <p>8 and another 25 hours since that time, correct?</p> <p>9 A Approximately 25 since that time, yeah.</p> <p>10 Q Let me ask you to look at your report and refer you to</p> <p>11 Pages 78 through 84.</p> <p>12 You identify 127 documents or other materials as</p> <p>13 references, correct?</p> <p>14 A Yes.</p> <p>15 Q Are those the materials that you are relying on to form</p> <p>16 the basis of your opinions in this case?</p> <p>17 A Yes, although there are different materials that I was</p> <p>18 able to review after the report was done, and they help</p> <p>19 support my opinion.</p> <p>20 Q And are those additional materials, materials that we</p> <p>21 have already discussed this morning?</p> <p>22 A Yes.</p> <p>23 Q Did the Plaintiffs' lawyers provide you with any of the</p> <p>24 references that are contained in Nos. 1 through 127?</p> <p>25 A I believe some of them they provided if it was one that I</p>
<p style="text-align: right;">Page 27</p> <p>1 Q From start to finish did you work in the same file to</p> <p>2 draft this report or did you have different files or</p> <p>3 drafts?</p> <p>4 A I copied different drafts as a way of backing up.</p> <p>5 Q Have you maintained the drafts, the iterations, as it</p> <p>6 went along?</p> <p>7 A Yes.</p> <p>8 Q How many hours would you say you have spent preparing the</p> <p>9 litigation report since the winter of 2016 to the spring</p> <p>10 of 2017 when you started writing it?</p> <p>11 A I would say approximately 240 hours.</p> <p>12 Q And on what do you base that estimate?</p> <p>13 A On invoices that I submitted through December 2018, plus</p> <p>14 an additional 25 hours since that time.</p> <p>15 Q I take it from your last answer, that up through December</p> <p>16 2018 you billed 240 hours total; is that accurate?</p> <p>17 A No.</p> <p>18 As of December 2018 I believe it was 211 hours.</p> <p>19 Q And is that 211 hours the total amount of time that you</p> <p>20 have spent grappling with the issues in this litigation</p> <p>21 or is that just the time that you have spent writing the</p> <p>22 report?</p> <p>23 MS. PARFITT: Objection; form.</p> <p>24 You may answer.</p> <p>25 THE WITNESS: It was since the time I</p>	<p style="text-align: right;">Page 29</p> <p>1 couldn't obtain on my own.</p> <p>2 A few of the mechanistic studies, I believe.</p> <p>3 Q If you can identify them by number, that would be good.</p> <p>4 A Yeah.</p> <p>5 Well, certainly some of the depositions I had no-- I</p> <p>6 did not access myself, so No. 77, 78, 79.</p> <p>7 The Longo reports, so 79 through 83.</p> <p>8 84 as well they provided.</p> <p>9 Q Anything else?</p> <p>10 A I am trying to search.</p> <p>11 They sent me some of the IARC monographs, but I had</p> <p>12 access previously to them myself, so I'm not sure which</p> <p>13 way you would want to count that, if I accessed the IARC</p> <p>14 myself online, but that-- Ms. Parfitt also sent their</p> <p>15 copy of it, so from two sources I had the same things.</p> <p>16 These are the IARC monographs, "The evaluation of</p> <p>17 carcinogenic effects," No. 40 and 42.</p> <p>18 I think there was a third IARC report.</p> <p>19 Q Would that be No. 74?</p> <p>20 A Yes.</p> <p>21 Q Other than items 40, 42, 74, and 75 through 84, are there</p> <p>22 any other materials that were provided to you by</p> <p>23 plaintiffs' counsel?</p> <p>24 A I am searching here.</p> <p>25 Some of the mechanistic studies they were able to</p>

<p style="text-align: right;">Page 30</p> <p>1 provide when I couldn't get them myself, and some of</p> <p>2 these journals were journals that were difficult to get,</p> <p>3 so I believe 85 and 90.</p> <p>4 Q Had you identified Items 85 and 90 prior to the time they</p> <p>5 were provided to you or did Counsel simply provide them</p> <p>6 to you?</p> <p>7 A No, I don't think they-- no, they didn't simply provide</p> <p>8 them to me.</p> <p>9 At the time that I added these, these were added</p> <p>10 toward the end of the time that I was preparing the</p> <p>11 report.</p> <p>12 I was able to see some other expert reports. One</p> <p>13 was a gynecologist -- I believe it was Plunkett -- who</p> <p>14 mentioned that there were-- that-- the issue of</p> <p>15 transporting had some additional references that I did</p> <p>16 not have.</p> <p>17 I had, originally, some mechanism-related papers</p> <p>18 related to migration of talcum powder products through</p> <p>19 the vaginal tract, and I didn't-- there were some</p> <p>20 additional ones here that I had not known about.</p> <p>21 I believe Egli and Sjosten were two-- sorry, 85 and</p> <p>22 90.</p> <p>23 Q References 77 through 84 appear to be deposition</p> <p>24 transcript exhibits and expert reports in litigation.</p> <p>25 Do you see that?</p>	<p style="text-align: right;">Page 32</p> <p>1 A Yes.</p> <p>2 Q Have you read all of those items?</p> <p>3 A Not in full.</p> <p>4 Do you want me to go through them one at a time?</p> <p>5 Q Let me just ask you generally, what's the difference</p> <p>6 between the references to your report and the items</p> <p>7 listed as additional materials and data considered? Why</p> <p>8 did you spread them out like that?</p> <p>9 A These up to 127 were available at the time that I was</p> <p>10 actively writing my report.</p> <p>11 Some of these other documents came along later and</p> <p>12 were available to me, so the counsel did provide them.</p> <p>13 Some of them were-- some of them were earlier, these</p> <p>14 Fletcher papers on-- on some of the mechanistic work was</p> <p>15 done earlier.</p> <p>16 Many of these are-- to my knowledge they were</p> <p>17 exhibits that were available from the case from the law</p> <p>18 firm.</p> <p>19 One of these is a repeat. 38 was listed originally.</p> <p>20 I think there's a little bit of variability here.</p> <p>21 Q Let me stop you there for a moment.</p> <p>22 A Yes.</p> <p>23 Q Did you read each of the 113 items in their entirety?</p> <p>24 A No, I did not.</p> <p>25 Q In describing the difference between the additional</p>
<p style="text-align: right;">Page 31</p> <p>1 A Yes.</p> <p>2 Q Have you reviewed all of those transcripts?</p> <p>3 A I skimmed 77 and 78 and looked at some of the exhibits</p> <p>4 that they had with them.</p> <p>5 I skimmed Longo, but I read through the November</p> <p>6 and-- this is another one-- these are not dated here-- of</p> <p>7 February and November.</p> <p>8 Q Let's take them one at a time on Longo.</p> <p>9 No. 79 says Longo, Rigler, April 2017.</p> <p>10 Did you review that?</p> <p>11 A Only skimming that.</p> <p>12 For all of these, I looked at the summary in the</p> <p>13 beginning, which presented the numbers of samples that</p> <p>14 were tested and the numbers that were considered to have</p> <p>15 asbestos.</p> <p>16 Q So you only reviewed the summaries; is that accurate?</p> <p>17 A Summaries, yes.</p> <p>18 Q And that applies to 77 through 83?</p> <p>19 A Through 83, yes.</p> <p>20 Q Take a look at Page 84 of your litigation report.</p> <p>21 Do you have that in front of you?</p> <p>22 A Yes.</p> <p>23 Q It lists here, "Additional materials and data</p> <p>24 considered," and it lists thereafter 113 items.</p> <p>25 Do you see that?</p>	<p style="text-align: right;">Page 33</p> <p>1 materials and data considered and the 127 references that</p> <p>2 we've already gone over, is it accurate to say that the</p> <p>3 additional materials were all provided by plaintiffs'</p> <p>4 counsel?</p> <p>5 MS. PARFITT: Objection to form.</p> <p>6 THE WITNESS: It's not true.</p> <p>7 Some of these I had myself--</p> <p>8 Q (By Mr. Williams) Could you please identify all of the</p> <p>9 items on here, of the 113 items, that you had yourself</p> <p>10 prior to them being provided by plaintiffs' counsel?</p> <p>11 A Okay. No. 2, American Cancer Society, I accessed their</p> <p>12 website several times.</p> <p>13 31 is a Hartge paper on talc and ovarian cancer, so</p> <p>14 I accessed that myself.</p> <p>15 This isn't a Hartge paper title, so that's one</p> <p>16 problem, one reason I'm struggling here, so I assume that</p> <p>17 this is another review that she has written, Hartge, but</p> <p>18 I'm not sure if it's the same as the paper that I</p> <p>19 referenced as one of my case-control studies that are</p> <p>20 referenced.</p> <p>21 The same issue with 33, 34 because I did reference</p> <p>22 Henderson, these are migration papers, so I'm not sure</p> <p>23 about that.</p> <p>24 No. 37 I do consider. It was a subset of the other</p> <p>25 Huncharek review, so I did see this earlier. I just did</p>

<p style="text-align: right;">Page 34</p> <p>1 not reference it for my report.</p> <p>2 38 is the same IARC monograph paper-- work that is</p> <p>3 referenced in the paper.</p> <p>4 Institute of Medicine I was not able to review.</p> <p>5 These other things look like they are Johnson &amp;</p> <p>6 Johnson or-- no-- other industry documents.</p> <p>7 Q Let me stop you there for a moment.</p> <p>8 Remember, my question is simply:</p> <p>9 Of the 113 items, please just list the numbers that</p> <p>10 you had before they were provided by Plaintiffs' counsel.</p> <p>11 That's all I need.</p> <p>12 A Okay. Sorry.</p> <p>13 67 I had previously, 79, 80, 87, 88, 89, 90, 91.</p> <p>14 92 I believe I referenced earlier, so 92, 93, 94,</p> <p>15 100-- can you remind me, is this for-- to distinguish</p> <p>16 what was in my report or what I obtained on my own?</p> <p>17 Q What you obtained on your own.</p> <p>18 A Okay. 103 I obtained on my own.</p> <p>19 That's it.</p> <p>20 Q All of the items, other than those that you just listed,</p> <p>21 were provided to you by Plaintiffs' counsel, correct?</p> <p>22 A I believe so, yes.</p> <p>23 Q You did not read each and every page of the materials</p> <p>24 that were provided to you by Plaintiffs' counsel; is that</p> <p>25 true?</p>	<p style="text-align: right;">Page 36</p> <p>1 Q Is that how you phrased it, "what available evidence</p> <p>2 there was"?</p> <p>3 A As the questions came along of various-- of parts of</p> <p>4 data-- so this came up with a question of what other</p> <p>5 constituents are there in Johnson &amp; Johnson Baby Powder</p> <p>6 and Shower to Shower, and I relied first on published</p> <p>7 data from Blount and Gordon, but I was interested in what</p> <p>8 other testing had been done to see what are the</p> <p>9 constituents, because otherwise there's no information,</p> <p>10 but it was a very general question. I didn't know what</p> <p>11 was available.</p> <p>12 Q In response to that question that you just described, the</p> <p>13 items that are listed here and the numbers that I just</p> <p>14 gave you, 40 through 47 for Imerys-- excuse me, 40</p> <p>15 through 46 for Imerys, and 47 through 65 for Johnson &amp;</p> <p>16 Johnson, are the only documents that were provided to</p> <p>17 you?</p> <p>18 MS. PARFITT: Objection.</p> <p>19 THE WITNESS: For that, I would also</p> <p>20 have received Longo, but one issue is I don't know-- from</p> <p>21 looking at these numbers, I don't have them memorized</p> <p>22 what they are.</p> <p>23 I would have to look them up.</p> <p>24 I do know that the Longo reports are the results of</p> <p>25 testing of constituents of the products.</p>
<p style="text-align: right;">Page 35</p> <p>1 A I did not, that's true.</p> <p>2 Q Let me direct your attention to No. 47 through 65 on the</p> <p>3 list that begin with the letters JNJ.</p> <p>4 Do you see that?</p> <p>5 A Yes.</p> <p>6 Q Do you understand that these are internal Johnson &amp;</p> <p>7 Johnson documents?</p> <p>8 Is that right?</p> <p>9 A I believe you.</p> <p>10 I don't know what they are from looking at just the</p> <p>11 numbers. I would have to reference back to my documents.</p> <p>12 Q No. 40 through 46 all start with the word Imerys,</p> <p>13 I-M-E-R-Y-S.</p> <p>14 Do you see those?</p> <p>15 A Yes.</p> <p>16 Q Do you understand those to be internal Imerys documents?</p> <p>17 A Again, I would have to look and see what they look like.</p> <p>18 Q Did you ask Plaintiffs' counsel to provide you with the</p> <p>19 Imerys and Johnson &amp; Johnson documents?</p> <p>20 A No, I did not.</p> <p>21 Q So they just gave those to you?</p> <p>22 A I asked to see what available evidence there was, and</p> <p>23 the-- the evidence that had been collected for the case</p> <p>24 in general, so that was a very general question, and they</p> <p>25 provided these.</p>	<p style="text-align: right;">Page 37</p> <p>1 Q (By Mr. Williams) And as you sit here today, you do not</p> <p>2 know whether or not the documents that are listed in</p> <p>3 References 40 through 65 are in fact authentic documents</p> <p>4 of Johnson &amp; Johnson or of Imerys, right, one way or the</p> <p>5 other?</p> <p>6 MS. PARFITT: Objection; form.</p> <p>7 THE WITNESS: I don't have memorized</p> <p>8 what these are.</p> <p>9 Q (By Mr. Williams) Pardon me?</p> <p>10 A I don't have memorized what these are, what these numbers</p> <p>11 refer to.</p> <p>12 Q With respect to any of the internal company documents</p> <p>13 that you have reviewed from either Imerys or Johnson &amp;</p> <p>14 Johnson, as you sit here now, you do not know whether any</p> <p>15 of those documents are in fact authentic Johnson &amp;</p> <p>16 Johnson or Imerys documents, correct?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 THE WITNESS: When I looked at any of</p> <p>19 these documents that were provided, they had stickers on</p> <p>20 them, I noticed, like-- so exhibit numbers, so I assumed</p> <p>21 this were exhibit numbers for some litigation.</p> <p>22 That's all I know.</p> <p>23 Q (By Mr. Williams) Are you relying on any of those</p> <p>24 internal company documents to form the basis of your</p> <p>25 opinions in this case?</p>

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<p>1 MS. PARFITT: Objection; form, vague.</p> <p>2 THE WITNESS: I looked through them.</p> <p>3 I did not read them in enough detail to have them form</p> <p>4 the primary basis of my opinion.</p> <p>5 Q (By Mr. Williams) Do they form something other than a</p> <p>6 primary basis for your opinion?</p> <p>7 A They added to some-- to consideration of what might be</p> <p>8 contained in these products.</p> <p>9 Q Do you have any idea what percentage of the entire</p> <p>10 document production from Johnson &amp; Johnson these 18</p> <p>11 documents comprised?</p> <p>12 A I do not.</p> <p>13 Q When you asked Counsel to provide you with what some of</p> <p>14 the evidence was with respect to the question you were</p> <p>15 being asked to consider, did you ask for both evidence</p> <p>16 that tends to show that, for example, Johnson's Baby</p> <p>17 Powder contains asbestos, and for evidence that it does</p> <p>18 not contain asbestos?</p> <p>19 A I asked about totality of evidence.</p> <p>20 I didn't use the words, "Please show me where it</p> <p>21 contains and where it doesn't."</p> <p>22 One thing I'm interested in is if something contains</p> <p>23 it, that's very concerning to me, so whether it's 50</p> <p>24 samples out of 100 that have asbestos in it, I would be</p> <p>25 concerned, but if it's only five, so even if more</p>	<p>1 question at issue?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: No, I don't-- well, it</p> <p>4 depends how you define a company, because occasionally if</p> <p>5 you're doing a full review of the scientific literature,</p> <p>6 you may-- for example, if you are doing a meta-analysis,</p> <p>7 they want to request data from other sources that aren't</p> <p>8 yet in the public domain, and if that study happens to be</p> <p>9 run through a company, then that could have happened.</p> <p>10 I can't say it's common.</p> <p>11 Typically we look at published data-- published</p> <p>12 scientific data from scientific opinions.</p> <p>13 Q (By Mr. Williams) When drafting a publication on a</p> <p>14 medical or a scientific question, have you ever sought</p> <p>15 internal company documents related to the subject matter?</p> <p>16 MS. PARFITT: Objection; asked and</p> <p>17 answered.</p> <p>18 THE WITNESS: So I'm curious, is that</p> <p>19 the same question as before? Did you just ask that</p> <p>20 question-- are you asking it again?</p> <p>21 Q (By Mr. Williams) I'll ask it another way.</p> <p>22 A Okay.</p> <p>23 Q Out of the multiple hundreds of publications that your</p> <p>24 resume lists with you as an author, how many cite to</p> <p>25 internal company documents?</p>
Page 39	Page 41
<p>1 negative samples were provided, and there's only five</p> <p>2 that are positive, that's still concerning.</p> <p>3 Q Were you provided any negative samples?</p> <p>4 A I did see evidence that some were negative, yes.</p> <p>5 Q Where did you see that?</p> <p>6 A I saw that in the Longo report, so there was-- each</p> <p>7 report had a different percent that were positive.</p> <p>8 Some were 50 percent positive, some 66 or 70 percent</p> <p>9 positive, so that means the inverse, 30 to 50 percent</p> <p>10 were negative, did not have asbestos.</p> <p>11 Also, from my perusal of the Johnson &amp; Johnson and</p> <p>12 Imerys documents that seem to be exhibits, it looked like</p> <p>13 there were some, but sometimes it was small amounts but</p> <p>14 sometimes it was larger, but that some contamination or</p> <p>15 inclusion of asbestos, but many times not.</p> <p>16 There was also an FDA website that was able to look</p> <p>17 at where they only tested, however, two products, two</p> <p>18 bottles of Johnson &amp; Johnson, and those were both</p> <p>19 negative.</p> <p>20 Q In the normal course of your work outside of litigation,</p> <p>21 do you review internal company documents for any reason?</p> <p>22 A No, not-- I would not have a reason to do that.</p> <p>23 Q When setting out to conduct research on a medical or</p> <p>24 other scientific question, outside of litigation, have</p> <p>25 you ever sought internal company documents related to the</p>	<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: I believe that none do.</p> <p>3 Most of my papers are with data from my own studies.</p> <p>4 Q (By Mr. Williams) Now, you were asked in this matter to</p> <p>5 review the current state of scientific literature</p> <p>6 regarding talcum powder products and to opine on whether</p> <p>7 those products cause ovarian cancer.</p> <p>8 Is that accurate?</p> <p>9 A Yes. I was asked to do a causal analysis and to form an</p> <p>10 opinion on the association between use of talcum powder</p> <p>11 products and risk of ovarian cancer.</p> <p>12 Q Were you given any other questions to answer or opine on?</p> <p>13 A So I'm just looking at your question. I'm sorry.</p> <p>14 I think this summarizes the question I was asked to</p> <p>15 answer.</p> <p>16 Q You were not retained to provide an opinion about whether</p> <p>17 or not talc can cause pleural or peritoneal mesothelioma,</p> <p>18 were you?</p> <p>19 A I was not, no.</p> <p>20 Q And you are not in fact providing an opinion on that</p> <p>21 subject?</p> <p>22 A I am not.</p> <p>23 Q Did you in fact review what you believe to be the current</p> <p>24 state of scientific literature regarding the question of</p> <p>25 whether talc can cause ovarian cancer?</p>



<p style="text-align: right;">Page 42</p> <p>1 A Yes, I believe I did.</p> <p>2 Q Did you consider literature and sources that refuted an</p> <p>3 association or causal association between talc and</p> <p>4 ovarian cancer?</p> <p>5 A Yes, I did.</p> <p>6 I looked at the entirety of literature as I knew</p> <p>7 it-- as I was able to find it.</p> <p>8 Q Did you consider literature and sources that have</p> <p>9 concluded that the totality of the scientific evidence is</p> <p>10 insufficient to find a causal association between talc</p> <p>11 and ovarian cancer?</p> <p>12 MS. PARFITT: Objection; form.</p> <p>13 THE WITNESS: Yes.</p> <p>14 Q (By Mr. Williams) When you wrote your report setting</p> <p>15 forth your opinions in this case, did you identify the</p> <p>16 sources that refuted the propositions that you were</p> <p>17 making?</p> <p>18 A Those papers would have been part of my report, yes.</p> <p>19 Q So is it your testimony that the report that you have in</p> <p>20 front of you, Exhibit No. 2, actually identifies the</p> <p>21 sources that refuted the propositions that you were</p> <p>22 making?</p> <p>23 A Yes.</p> <p>24 If these were papers that included data-- so I use</p> <p>25 data-- I reviewed the data from these studies, and</p>	<p style="text-align: right;">Page 44</p> <p>1 It's in the table, and in the report I did note</p> <p>2 where there was a dose response note-- I did note whether</p> <p>3 there was a dose response seen in the paper.</p> <p>4 I can't-- let me see, I can look through-- I'm not</p> <p>5 sure if you want me to look through for each--</p> <p>6 Q We'll do that a little later.</p> <p>7 A Okay.</p> <p>8 Q Let me ask you now to turn to Page 68 of your report with</p> <p>9 the heading that says, "Conclusion."</p> <p>10 A (Witness complies.)</p> <p>11 Q Do you have that in front of you?</p> <p>12 A Yes.</p> <p>13 Q Does that conclusion accurately summarize your opinion in</p> <p>14 this case on the question of whether or not perineal use</p> <p>15 of talcum powder products can cause ovarian cancer?</p> <p>16 A Yes.</p> <p>17 Q Now, your opinion is stated to a, quote, "medical and</p> <p>18 scientific degree of certainty," closed quote.</p> <p>19 Do you see that?</p> <p>20 A Yes.</p> <p>21 Q What do you mean by the use of the term "degree" in that</p> <p>22 sentence?</p> <p>23 A I would say a high degree.</p> <p>24 I don't put percentages on my opinion. It's not</p> <p>25 typical in my field to do that, but I would say with a</p>
<p style="text-align: right;">Page 43</p> <p>1 regardless of what those studies concluded, I included</p> <p>2 them in the report.</p> <p>3 Q Did you discuss in your report the part or parts within</p> <p>4 those sources that refuted the propositions you were</p> <p>5 making, including the data?</p> <p>6 A I believe that I discussed in general that-- whether</p> <p>7 there is evidence of a causal relationship between talcum</p> <p>8 powder product use and risk of ovarian cancer.</p> <p>9 I did not, for each paper, reiterate what they</p> <p>10 concluded. I looked at their data.</p> <p>11 Q If there were parts of a study, for instance, that did</p> <p>12 not support one of your opinions, did you make a note of</p> <p>13 that in your report?</p> <p>14 MS. PARFITT: Objection; form.</p> <p>15 THE WITNESS: If the studies did not</p> <p>16 show an association between talcum powder product use and</p> <p>17 risk of ovarian cancer, I included those data, yes.</p> <p>18 I included it both in the content of the report as</p> <p>19 well as in the data table that I included at the end of</p> <p>20 the report, and I included those data.</p> <p>21 Q (By Mr. Williams) If those data did not, for instance,</p> <p>22 show a dose response related to exposure to talcum powder</p> <p>23 and the incidence of ovarian cancer, did you note in your</p> <p>24 report where the data did not support dose response?</p> <p>25 A I did note that.</p>	<p style="text-align: right;">Page 45</p> <p>1 high degree of certainty that based on the totality of</p> <p>2 evidence, that use of talcum powder products can cause</p> <p>3 ovarian cancer.</p> <p>4 Q Do you believe that perineal use of talcum powder</p> <p>5 products manufactured today, in 2019, can cause ovarian</p> <p>6 cancer?</p> <p>7 A So talcum powder products, yes.</p> <p>8 There's no evidence that it would have changed.</p> <p>9 The evidence from the epidemiologic studies were</p> <p>10 from people's use decades previously, but then looking at</p> <p>11 contents of talcum powder products over time it looks</p> <p>12 like they continue to have constituents that could be</p> <p>13 carcinogenic, as well as talcum powder by itself has been</p> <p>14 shown to be carcinogenic, and so I believe that if</p> <p>15 somebody was using them today, they could still have the</p> <p>16 same potential for developing ovarian cancer as if they</p> <p>17 used them 50 years ago.</p> <p>18 Q So the answer to my question is that you believe that</p> <p>19 perineal use of talcum powder products manufactured</p> <p>20 today, in 2019, can cause ovarian cancer, correct?</p> <p>21 A Yes-- yes.</p> <p>22 Q Did you reach the opinion, to a degree of medical and</p> <p>23 scientific certainty, that perineal use of talcum powder</p> <p>24 products can cause ovarian cancer before or after you</p> <p>25 were hired by Plaintiffs' counsel?</p>

<p style="text-align: right;">Page 46</p> <p>1 A After I had conducted a full systematic review of the</p> <p>2 epidemiology data and mechanistic data, including</p> <p>3 biologic evidence, and then done a causal analysis,</p> <p>4 that's when I concluded that these products could</p> <p>5 increase-- could cause ovarian cancer.</p> <p>6 Q So the answer is after you were hired by Plaintiffs'</p> <p>7 counsel; is that correct?</p> <p>8 MS. PARFITT: Objection; misstates her</p> <p>9 testimony, asked and answered.</p> <p>10 Q (By Mr. Williams) I am looking for a temporal answer.</p> <p>11 So my question is:</p> <p>12 Did you reach your conclusions before or after you</p> <p>13 were retained by Plaintiffs' counsel?</p> <p>14 MS. PARFITT: Objection; form, asked</p> <p>15 and answered.</p> <p>16 THE WITNESS: It was after I had done</p> <p>17 the causal analysis.</p> <p>18 Q (By Mr. Williams) And that was after you were retained?</p> <p>19 MS. PARFITT: Objection.</p> <p>20 THE WITNESS: That was after I did the</p> <p>21 causal analysis, which was after I began this project</p> <p>22 with Counsel.</p> <p>23 Q (By Mr. Williams) Did you consider whether some brands</p> <p>24 of talcum powder products can cause ovarian cancer but</p> <p>25 others may not?</p>	<p style="text-align: right;">Page 48</p> <p>1 cause ovarian cancer.</p> <p>2 Q And that is true whether it's Johnson's Baby Powder or</p> <p>3 any other talcum powder product?</p> <p>4 MS. PARFITT: Objection; form.</p> <p>5 THE WITNESS: Yes.</p> <p>6 Q (By Mr. Williams) Is it your opinion that genital</p> <p>7 perineal use of Shower to Shower product specifically can</p> <p>8 cause ovarian cancer?</p> <p>9 A To my knowledge it includes both talc, and some percent</p> <p>10 may include asbestos and other constituents, and so that</p> <p>11 would be my opinion, yes.</p> <p>12 Q And same question:</p> <p>13 Even if Shower to Shower product did not contain</p> <p>14 asbestos, it is your conclusion that because it contains</p> <p>15 talc, it can cause ovarian cancer, correct?</p> <p>16 A Yes.</p> <p>17 Q And it's your testimony here today that it has been</p> <p>18 established, to a degree of medical and scientific</p> <p>19 certainty, that that is the case?</p> <p>20 A Yes.</p> <p>21 Q Is it your testimony today that it is accepted in the</p> <p>22 medical and scientific field that talcum powder causes</p> <p>23 ovarian cancer?</p> <p>24 MS. PARFITT: Objection; form.</p> <p>25 THE WITNESS: I would say that many</p>
<p style="text-align: right;">Page 47</p> <p>1 A The epidemiology data were insufficient to determine</p> <p>2 whether any particular brand was used by women, except</p> <p>3 for one study, Cramer, in 2016.</p> <p>4 It's my understanding that Johnson &amp; Johnson</p> <p>5 products had the vast proportion of the market share over</p> <p>6 time, but I did not come to a conclusion that any</p> <p>7 particular product was causing this.</p> <p>8 All I know is that use of these products by these</p> <p>9 women over time increased their risk for ovarian cancer</p> <p>10 and that it can cause ovarian cancer.</p> <p>11 Q So it is your opinion that genital perineal use of</p> <p>12 Johnson's Baby Powder specifically can cause ovarian</p> <p>13 cancer, correct?</p> <p>14 A Yes, given that it's been shown to contain asbestos,</p> <p>15 given that it contains talc, which has been shown to be</p> <p>16 carcinogenic, then I would say yes, it could be-- it</p> <p>17 could be a cause of ovarian cancer.</p> <p>18 Q Let me tease that out a little bit.</p> <p>19 If the product did not contain asbestos, is it your</p> <p>20 testimony that-- is it your opinion that genital perineal</p> <p>21 use of Johnson's Baby Powder can cause ovarian cancer</p> <p>22 without containing asbestos?</p> <p>23 A Yes, even without asbestos, my opinion is that talc can</p> <p>24 increase risk of ovarian cancer, that there are</p> <p>25 biological mechanisms, and so that these products could</p>	<p style="text-align: right;">Page 49</p> <p>1 scientists, many clinicians do believe that it can cause</p> <p>2 ovarian cancer.</p> <p>3 Q (By Mr. Williams) My question is different.</p> <p>4 My question is whether or not, Dr. McTiernan, it is</p> <p>5 accepted in the medical and scientific community today</p> <p>6 that exposure to talcum powder causes ovarian cancer.</p> <p>7 A And I think I'm having trouble with the word "accepted,"</p> <p>8 so I am not sure specifically what you mean that it was</p> <p>9 "accepted."</p> <p>10 Who it is accepted by, does somebody have</p> <p>11 guidelines, is somebody giving advice to the public--</p> <p>12 there are lots of different organizations that you could</p> <p>13 call "the medical field," so I think that's why I'm</p> <p>14 having some trouble there.</p> <p>15 To me it's a question that's not specific enough for</p> <p>16 me to figure out how to answer it.</p> <p>17 Q Well, it's one thing if there is a person in the medical</p> <p>18 or scientific field who holds an opinion and quite</p> <p>19 another to say that something is generally accepted in</p> <p>20 the medical and scientific community that a substance</p> <p>21 causes cancer; isn't that right?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 THE WITNESS: Yeah, I still have a</p> <p>24 problem with the word "accepted" because I work in many</p> <p>25 other areas, and I have seen that there are so many</p>

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<p>1 different opinions by clinicians, by scientists about</p> <p>2 associations, and then it comes to the point of policy</p> <p>3 and coming up with guidelines.</p> <p>4 That's why I am having a little problem answering a</p> <p>5 question of whether it's accepted.</p> <p>6 I think that for me what I can come up with is this</p> <p>7 is my opinion from the research that I've done.</p> <p>8 I can't speak for other medical groups of whatever</p> <p>9 you are talking about.</p> <p>10 I'm not sure which groups you are talking about.</p> <p>11 Q (By Mr. Williams) Wouldn't it be accurate to say,</p> <p>12 Dr. McTiernan, that it is, at best, inconsistent in terms</p> <p>13 of the medical and scientific community as to whether or</p> <p>14 not exposure to talcum powder in the perineal area causes</p> <p>15 ovarian cancer?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 THE WITNESS: Oh, I would say that any</p> <p>18 exposure, any medical treatment, any medical prevention</p> <p>19 method is going to be inconsistent, and I do know that</p> <p>20 IARC has classified talc, even talc without asbestos, as</p> <p>21 a possible carcinogen, and they have a pretty high bar</p> <p>22 for whether they're going to consider something a</p> <p>23 carcinogen, and they were talking about ovarian cancer</p> <p>24 specifically.</p> <p>25 Q (By Mr. Williams) We'll talk about that a little bit</p>	<p>1 causes ovarian cancer, isn't it accurate to say that that</p> <p>2 survey is at best inconsistent as to that conclusion?</p> <p>3 MS. PARFITT: Objection; form,</p> <p>4 misstates her testimony-- excuse me, it doesn't misstate</p> <p>5 her testimony. It's been asked and answered, clearly.</p> <p>6 THE WITNESS: I think-- I think from</p> <p>7 what you're asking is I've surveyed the medical community</p> <p>8 and scientific community, which I have not. I have not</p> <p>9 surveyed them.</p> <p>10 My job was to review studies to look at the</p> <p>11 epidemiologic data. That was my primary purpose.</p> <p>12 Then to look at biological mechanisms.</p> <p>13 And then to do a causal analysis.</p> <p>14 I did not contact and survey the medical community</p> <p>15 in this field, which could be vast because we are talking</p> <p>16 about gynecology, prevention, government bodies,</p> <p>17 epidemiology-- I just did not-- I was not asked to do</p> <p>18 that and I did not do that.</p> <p>19 Q (By Mr. Williams) In forming your opinion that perineal</p> <p>20 talc use can cause ovarian cancer, did you calculate how</p> <p>21 much talc is needed to cause ovarian cancer?</p> <p>22 A I looked at that. I was not able to determine because</p> <p>23 there's no-- no study has been able to collect</p> <p>24 information in enough depth to know how much the</p> <p>25 individual woman used, exactly how much in a particular</p>
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<p>1 later, but let me go back to my question.</p> <p>2 My question is whether or not it is at best</p> <p>3 inconsistent, in terms of looking across the available</p> <p>4 medical and scientific information regarding an</p> <p>5 association between talcum powder and causing ovarian</p> <p>6 cancer, to conclude that in fact talcum powder exposure</p> <p>7 in the perineal area causes ovarian cancer; isn't that</p> <p>8 true?</p> <p>9 MS. PARFITT: Objection; form.</p> <p>10 THE WITNESS: So I think I would feel</p> <p>11 a little better if you are talking now about across the</p> <p>12 evidence or across all of this research, all of these</p> <p>13 studies, and there were-- there have been 24 to 25</p> <p>14 case-control cohort studies that have looked at this</p> <p>15 information, and when you look at them in totality,</p> <p>16 either meta-analysis or pooled analysis, you really see</p> <p>17 clear evidence that ovarian cancer risk is higher in</p> <p>18 people who have-- and statistically significantly higher</p> <p>19 in people who have used these products.</p> <p>20 Q (By Mr. Williams) Let me ask you, for purposes of my</p> <p>21 question, to focus on the medical and scientific</p> <p>22 community, okay, not your personal opinion of the data.</p> <p>23 With respect to your survey of the medical and</p> <p>24 scientific community and its analysis of whether or not</p> <p>25 exposure to talcum powder in the perineal area actually</p>	<p>1 day she used, and what was the content of the particular</p> <p>2 bottle that she used or the bottle she used over time,</p> <p>3 and many of the studies did not also even include enough</p> <p>4 information to look at how frequently or how often they</p> <p>5 did, but once they did, then you could see if you had</p> <p>6 people that used it more often for a longer period of</p> <p>7 time, that's when there was even a great increase in</p> <p>8 risk, and that would be a dose response effect.</p> <p>9 Q Is the answer to my question "no," you did not calculate</p> <p>10 how much talc is needed to cause ovarian cancer?</p> <p>11 MS. PARFITT: Objection; form, asked</p> <p>12 and answered.</p> <p>13 Q (By Mr. Williams) I am not asking for the reasons.</p> <p>14 I am just asking for the bottom line.</p> <p>15 The bottom line is that you did not calculate how</p> <p>16 much talc is needed to cause ovarian cancer, correct?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 THE WITNESS: It was not possible to</p> <p>19 determine exactly how much talcum powder product was</p> <p>20 used, so therefore it's not possible to determine how</p> <p>21 much of each dose particular-- of a particular product</p> <p>22 increases risk.</p> <p>23 Q (By Mr. Williams) In your mind is there a dose of talc</p> <p>24 that does not cause ovarian cancer when applied</p> <p>25 perineally?</p>

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<p>1 A There's no evidence that there's any lower threshold</p> <p>2 than--</p> <p>3 Q I-- I'm sorry. I didn't mean to cut you off.</p> <p>4 A So the question is there a dose of--</p> <p>5 Q Is there a dose of talc that does not cause ovarian</p> <p>6 cancer when applied perineally?</p> <p>7 A There's no evidence that there's any lower limit to a</p> <p>8 dose-- to use of these products that could increase risk.</p> <p>9 Q It is your testimony here today that a single dose from a</p> <p>10 single perineal application of talc is enough to cause</p> <p>11 ovarian cancer based upon your review of the studies?</p> <p>12 A The studies did not give that level of detail, of whether</p> <p>13 somebody used one dose in terms of ovarian cancer risk.</p> <p>14 However, if you think of the biology, if this one</p> <p>15 dose was introduced perineal, then could move up through</p> <p>16 the vagina, through the cervix and the uterus, and get to</p> <p>17 just as far as the fallopian tubes, if it sits in there</p> <p>18 and causes an inflammatory reaction, theoretically one</p> <p>19 dose could be enough.</p> <p>20 Typically in epidemiologic studies we look for dose</p> <p>21 response, so if somebody is using something longer, more</p> <p>22 time, more frequently, that increases the chance that</p> <p>23 some of that content could get up into her perineal--</p> <p>24 sorry, her peritoneal, fallopian tubes, ovaries, but</p> <p>25 there's no reason that one dose couldn't do that.</p>	<p>1 MS. PARFITT: Objection; asked and</p> <p>2 answered.</p> <p>3 She has responded.</p> <p>4 THE WITNESS: I am saying I couldn't</p> <p>5 find data from the studies about one dose, the effect of</p> <p>6 one dose on ovarian cancer, but I am saying that one dose</p> <p>7 could cause inflammation.</p> <p>8 Q (By Mr. Williams) When you said "theoretically one dose</p> <p>9 could be enough," you were speculating, correct?</p> <p>10 MS. PARFITT: Objection; asked and</p> <p>11 answered, and she has given you the answer, Mr. Williams.</p> <p>12 THE WITNESS: I am saying I don't have</p> <p>13 the data to say exactly.</p> <p>14 Q (By Mr. Williams) You don't have the data to say one way</p> <p>15 or the other?</p> <p>16 MS. PARFITT: Objection; misstates her</p> <p>17 testimony.</p> <p>18 THE WITNESS: I don't have the data on</p> <p>19 ovarian cancer and one dose.</p> <p>20 MS. PARFITT: Mr. Williams, without</p> <p>21 breaking any train of thought, we have gone about an hour</p> <p>22 and 15 minutes. Maybe in an appropriate place, we could</p> <p>23 take a minute, but I don't want to break your stride.</p> <p>24 MR. WILLIAMS: In a minute. Thank</p> <p>25 you.</p>
Page 55	Page 57
<p>1 We do know from the biology that one dose of talc</p> <p>2 injected either into the pleura or into the lungs can</p> <p>3 cause an inflammatory response.</p> <p>4 Q When you say "theoretically one dose could be enough,"</p> <p>5 you are speculating; are you not?</p> <p>6 MS. PARFITT: Objection; misstates her</p> <p>7 testimony, form.</p> <p>8 THE WITNESS: I am saying that we know</p> <p>9 from other evidence, the biology, that if one dose is</p> <p>10 injected into the pleura, and I'm talking humans, or</p> <p>11 inhaled into the lungs, one dose can cause an</p> <p>12 inflammatory response, so that's why I believe one dose</p> <p>13 could cause a response in the peritoneal area-- sorry, in</p> <p>14 the fallopian tube or ovarian area.</p> <p>15 Q (By Mr. Williams) You used the phrase "theoretically one</p> <p>16 dose could be enough," did you not, in your answer a few</p> <p>17 moments ago?</p> <p>18 A I said that because it would be unethical to introduce</p> <p>19 one dose of this substance into the fallopian tubes or</p> <p>20 ovary area, so you couldn't test that in a human</p> <p>21 directly.</p> <p>22 Q My question is different, ma'am.</p> <p>23 My question is that you are the person in the room</p> <p>24 who used the phrase "theoretically one dose could be</p> <p>25 enough" just a few moments ago, correct?</p>	<p>1 Q (By Mr. Williams) When you said a few moments ago that</p> <p>2 you believe that even one dose could cause inflammation,</p> <p>3 based upon your review of the science, have you reviewed</p> <p>4 scientific literature, any study that says talcum powder</p> <p>5 causes inflammation, which inflammation causes ovarian</p> <p>6 cancer?</p> <p>7 A The evidence that I was able to look at, because you can</p> <p>8 not do-- ethically you cannot do a clinical trial where</p> <p>9 you expose women to talcum powder products in one group</p> <p>10 and a placebo in another and then follow them forward for</p> <p>11 30 or 40 years to see if you develop ovarian cancer--</p> <p>12 because that trial cannot be done, we have to look at</p> <p>13 different lines of evidence, so we look at the</p> <p>14 epidemiology, we look at whether materials can be</p> <p>15 introduced into the peritoneal area and make their way up</p> <p>16 through the vaginal tract and get to the fallopian tubes</p> <p>17 or ovaries, and then we know that inflammation does</p> <p>18 increase risk for ovarian cancer.</p> <p>19 There have been many studies that show that</p> <p>20 individuals with high levels of inflammatory markers in</p> <p>21 their blood, for example, have increased risk for ovarian</p> <p>22 cancer, and people with inflammatory conditions, again,</p> <p>23 endometriosis, are at an increased risk for ovarian</p> <p>24 cancer.</p> <p>25 Q Does all inflammation cause cancer, ma'am?</p>

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<p>1 A It's not clear that all does, but it certainly increases</p> <p>2 risk.</p> <p>3 Q So the answer is "no," not all inflammation causes</p> <p>4 cancer?</p> <p>5 MS. PARFITT: Objection; misstates her</p> <p>6 testimony.</p> <p>7 THE WITNESS: I am saying that the</p> <p>8 inflammation-- increased inflammation is associated with</p> <p>9 increased risk for cancer.</p> <p>10 Q (By Mr. Williams) What types of cancer?</p> <p>11 A For example, some inflammatory conditions like Crohn's</p> <p>12 disease increases risk for colon cancer.</p> <p>13 Individuals with rheumatoid arthritis have increased</p> <p>14 risk for lymphoma.</p> <p>15 Those inflammatory markers that I mentioned, like</p> <p>16 C-reactive protein and to interleukin 6 or 8, if those</p> <p>17 are increased, all those are can increase risk for breast</p> <p>18 cancer, ovarian cancer, colon cancer, and other cancers.</p> <p>19 Q Now, you have a medical degree, correct?</p> <p>20 A Mm-hm.</p> <p>21 Q Is that a "yes"?</p> <p>22 A Yes.</p> <p>23 Q And you held a license to practice medicine in the state</p> <p>24 of Washington from July of 1991 to February 18th of 2018;</p> <p>25 is that right?</p>	<p>1 there.</p> <p>2 The work I do for the World Cancer Research Fund</p> <p>3 looks at association of diet and physical activity and</p> <p>4 obesity, and risk of cancer and ovarian cancer is one of</p> <p>5 those.</p> <p>6 Q I didn't mean to include the work you have done on the</p> <p>7 World Cancer Research Fund. I meant separately published</p> <p>8 articles of the sort that are referenced on your CV.</p> <p>9 Did you understand that to be my question?</p> <p>10 A Yes.</p> <p>11 So the first one is in press for 2019, for March of</p> <p>12 2019, and ovarian was one of those cancers.</p> <p>13 Q And where is that to be published?</p> <p>14 A Medicine &amp; Science in Sports &amp; Exercise.</p> <p>15 Q Have you ever given any lectures regarding talcum powder</p> <p>16 products and ovarian cancer?</p> <p>17 A No, I have not.</p> <p>18 Q Have you ever given any presentations regarding talcum</p> <p>19 powder products and ovarian cancer?</p> <p>20 A No, I haven't.</p> <p>21 Q Have you ever posted on social media at all regarding</p> <p>22 talcum powder products and ovarian cancer?</p> <p>23 A I don't believe so.</p> <p>24 Q Have you ever written any textbook chapters regarding</p> <p>25 talcum powder products and ovarian cancer?</p>
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<p>1 A I apologize, it's still active. I still have a license.</p> <p>2 Q And you held what's known as a DEA license that allows</p> <p>3 one to prescribe medicines?</p> <p>4 A Yes.</p> <p>5 Q Is that still active?</p> <p>6 A That's still active, yes.</p> <p>7 Q Is it accurate to say that you have never been a</p> <p>8 gynecological oncologist?</p> <p>9 A That's accurate.</p> <p>10 Q Now, you have written two articles about how diet and</p> <p>11 exercise affect women after they have been diagnosed with</p> <p>12 gynecologic cancer, correct?</p> <p>13 A At least two, yeah.</p> <p>14 Q None of the articles that you've written on that topic</p> <p>15 studied what causes or may cause gynecological cancers;</p> <p>16 is that true?</p> <p>17 A That's correct.</p> <p>18 Q Can we agree that you have never written any</p> <p>19 peer-reviewed, published article or study on the causes</p> <p>20 of ovarian cancer?</p> <p>21 A If we're talking about an overall general article, that's</p> <p>22 true.</p> <p>23 However, we have a paper in press that is looking at</p> <p>24 the association of physical activity with various</p> <p>25 cancers, and ovarian cancer was one that was included</p>	<p>1 A No, I haven't.</p> <p>2 Q You are not and were not ever an oncologist of any kind?</p> <p>3 A No.</p> <p>4 Q You are not a pathologist, correct?</p> <p>5 A No.</p> <p>6 Q You are not a cancer biologist, right?</p> <p>7 A No.</p> <p>8 Q You are not a toxicologist?</p> <p>9 A No.</p> <p>10 Q You are not an industrial hygienist?</p> <p>11 A No.</p> <p>12 Q Prior to being hired by the Plaintiffs' lawyers in talc</p> <p>13 litigation, you had not personally conducted research on</p> <p>14 talcum powder product use and risk for ovarian cancer,</p> <p>15 true?</p> <p>16 MS. PARFITT: Objection; misstates her</p> <p>17 testimony, form.</p> <p>18 THE WITNESS: Let me look at the--</p> <p>19 prior to being hired-- it depends on what you consider</p> <p>20 research because I had read some articles, but I had not</p> <p>21 produced a report in that area.</p> <p>22 Q (By Mr. Williams) Let me put it this way:</p> <p>23 You have published several manuscripts on</p> <p>24 gynecologic cancers, including the prevention of ovarian</p> <p>25 cancer in women at high genetic risk, correct?</p>



Page 62	Page 64
<p>1 A Yes.</p> <p>2 Q And you have published manuscripts regarding the effects</p> <p>3 of weight and exercise on the risk for ovarian cancer,</p> <p>4 correct?</p> <p>5 A Yes.</p> <p>6 Q But you have not personally conducted research on talcum</p> <p>7 powder use and risk for ovarian cancer, correct?</p> <p>8 MS. PARFITT: Objection.</p> <p>9 THE WITNESS: The report that I've</p> <p>10 just prepared I would say is research because it was a</p> <p>11 systematic review.</p> <p>12 Q (By Mr. Williams) Let me have you look at Exhibit No. 2,</p> <p>13 your report, and then we'll take a break in a minute.</p> <p>14 A (Witness complies.)</p> <p>15 Q Could you turn to Page 6, please?</p> <p>16 The first full paragraph on Page 6 begins by saying,</p> <p>17 "Although I have not personally conducted research on</p> <p>18 talcum powder product use and risk for ovarian cancer, I</p> <p>19 have published several manuscripts," and it goes on.</p> <p>20 Do you see that?</p> <p>21 A Yes.</p> <p>22 Q Is the first clause in that sentence true or not true?</p> <p>23 A Yes, that's true.</p> <p>24 Q Let's just mark, before we take a break, these other</p> <p>25 items we said we were going to mark.</p>	<p>1 Q (By Mr. Williams) Dr. McTiernan, before you were ever</p> <p>2 retained as a paid consultant for this litigation in the</p> <p>3 fall of 2016, you had written literally hundreds of</p> <p>4 articles for peer-reviewed journals.</p> <p>5 Is that true?</p> <p>6 A Yes.</p> <p>7 Q You have worked on comprehensive written reports for the</p> <p>8 U.S. government in your career?</p> <p>9 A Yes.</p> <p>10 Q Can you just describe very briefly, if you would, the</p> <p>11 types?</p> <p>12 A The U.S. government, I did two reports on physical</p> <p>13 activity and cancer risk and survival, 2008 and 2018, so</p> <p>14 this was the-- it's called a physical activity guidelines</p> <p>15 advisory committee, and for that we relied on</p> <p>16 meta-analyses. We did not do our own research.</p> <p>17 I've also over the years done grant reviews for the</p> <p>18 government. I have reviewed their intramural program, so</p> <p>19 that means their science, have reviewed their science,</p> <p>20 and I have prepared reports years ago for National Cancer</p> <p>21 Institute for-- I've done grant reviews for other</p> <p>22 country's governments.</p> <p>23 That's my governmental service.</p> <p>24 I was on-- sorry, the United States government</p> <p>25 still-- grant reviews for the Department of Defense and</p>
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<p>1 First is Exhibit No. 3, we would like to mark it,</p> <p>2 "Additional materials to Dr. Anne McTiernan."</p> <p>3 (Exhibit No. 3 marked</p> <p>4 for identification.)</p> <p>5</p> <p>6 Q (By Mr. Williams) Now, I think you told us that the</p> <p>7 additional materials that you brought here today support</p> <p>8 your opinions; is that correct?</p> <p>9 A Yes.</p> <p>10 Q Other than believing that those materials you brought</p> <p>11 today support your opinions with respect to the</p> <p>12 association between perineal talcum powder use and</p> <p>13 ovarian cancer, have your opinions changed at all since</p> <p>14 you first prepared your report that we've marked as</p> <p>15 Exhibit No. 2?</p> <p>16 A No, they have not.</p> <p>17 MR. WILLIAMS: Thanks. Let's take a</p> <p>18 quick break, about ten minutes.</p> <p>19 VIDEOGRAPHER: Going off the record,</p> <p>20 the time is 10:28 a.m.</p> <p>21 (Recess 10:28 to 10:40 a.m.)</p> <p>22</p> <p>23 VIDEOGRAPHER: The time is 10:40 a.m.</p> <p>24 We are back on the record. This is the start of Media</p> <p>25 Unit 2.</p>	<p>1 the National Institute of Health.</p> <p>2 Q Let me ask you to look in your report, Exhibit No. 2, at</p> <p>3 Page No. 7.</p> <p>4 In the section of your report entitled, "Overall</p> <p>5 approach," you write, in the second sentence, "I drew</p> <p>6 upon my years of experience with synthesizing and</p> <p>7 interpreting large numbers of epidemiologic studies for</p> <p>8 comprehensive reports, including work for the U.S.</p> <p>9 government," and we have gone through that, right?</p> <p>10 A Mm-hm.</p> <p>11 Q Is that a "yes"?</p> <p>12 A Yes. Sorry.</p> <p>13 Q You go on to say, "the World Health Organization,</p> <p>14 International Agency for Research on Cancer"-- IARC,</p> <p>15 correct?</p> <p>16 A Yes.</p> <p>17 Q --"and the World Cancer Research Fund," correct?</p> <p>18 A Yes.</p> <p>19 Q And you have drawn upon your experience with all of those</p> <p>20 organizations in setting forth your conclusions here?</p> <p>21 A Yes.</p> <p>22 Q And that's what you write in your report?</p> <p>23 A Yes.</p> <p>24 Q And you write that your opinions are based on the</p> <p>25 published epidemiologic evidence, including original</p>

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<p>1 case-control and cohort studies, systematic reviews,</p> <p>2 meta-analyses, and pooled analyses on the topic of talcum</p> <p>3 powder products exposure and a risk of ovarian cancer,</p> <p>4 correct?</p> <p>5 A Yes, that's what I wrote.</p> <p>6 Q Okay. For the World Cancer Research Fund, you are a</p> <p>7 member of the advisory panel of experts that guides</p> <p>8 interpretation of meta-analyses and systematic reviews of</p> <p>9 nutrition, physical activity, obesity, and risk for many</p> <p>10 cancers, correct?</p> <p>11 A Yes, that's correct.</p> <p>12 Q On Page 5, if you flip one page earlier, you reference,</p> <p>13 in the section of your report citing your credentials,</p> <p>14 the work that you have done for the World Cancer Research</p> <p>15 Fund, right?</p> <p>16 A Yes.</p> <p>17 Q In the middle of the page on Page 5 of Exhibit No. 2 you</p> <p>18 say, "For the World Cancer Research Fund, I am a member</p> <p>19 of the advisory panel of experts that guides</p> <p>20 interpretation of meta-analyses and systematic reviews of</p> <p>21 nutrition, physical activity, obesity, and risk for many</p> <p>22 cancers, including ovarian cancer," right?</p> <p>23 A Yes.</p> <p>24 Q And you have a link there to an ovarian cancer 2014</p> <p>25 report that you did, right?</p>	<p>1 cancers.</p> <p>2 I can't say who wrote them because I never quite</p> <p>3 know who exactly did what-- what one person did the main</p> <p>4 report drafting.</p> <p>5 Q As a panel member, you read the reports though, right?</p> <p>6 A Yes.</p> <p>7 Q As a panel member you make recommendations based on the</p> <p>8 reports, don't you?</p> <p>9 A Say it again--</p> <p>10 Q As a panel member--</p> <p>11 A You make recommendations-- that means to them or to--</p> <p>12 Q To the public.</p> <p>13 Let me rephrase the question.</p> <p>14 As a panel member for the World Cancer Research</p> <p>15 Fund, the WCRF, you read the reports that are prepared by</p> <p>16 that organization and make recommendations to the public</p> <p>17 based upon those reports, right?</p> <p>18 A I do read the reports. I give input because I'm part of</p> <p>19 a panel. It doesn't mean I can drive exactly what gets</p> <p>20 sent there.</p> <p>21 When the public recommendations come out, we are</p> <p>22 given a set of guidelines that if there are</p> <p>23 recommendations that are developed, they will be</p> <p>24 standardized, and we are asked to follow those standards.</p> <p>25 I cannot develop my own standards for what</p>
Page 67	Page 69
<p>1 A Yes.</p> <p>2 Q And that--</p> <p>3 A Maybe I could correct that.</p> <p>4 I'm on the advisory panel. I don't prepare those</p> <p>5 reports.</p> <p>6 I help interpret them, but it's the World Cancer</p> <p>7 Research Fund scientists-- sorry, Imperial College does</p> <p>8 the meta-analyses and the systematic reviews, and then</p> <p>9 the World Cancer Research Fund has scientists that write</p> <p>10 the reports.</p> <p>11 As an advisory committee member, I give opinions</p> <p>12 on-- with the rest of the committee on-- and we summarize</p> <p>13 what we think we are seeing in those-- in the data.</p> <p>14 Q So just to make sure that I understand the process, the--</p> <p>15 you mentioned that there are staff members, I suppose,</p> <p>16 from Imperial College who actually write the reports?</p> <p>17 A The staff members-- the scientists from Imperial College</p> <p>18 do the meta-analyses. They collect the data from all</p> <p>19 available studies, and they prepare data tables, and</p> <p>20 there are scientists at World Cancer Research Fund-- so</p> <p>21 it's a funding organization and a scientific</p> <p>22 organization, so their scientists write the reports.</p> <p>23 For some of these cancers they also contract to</p> <p>24 the-- to IARC, to scientists there who will write some of</p> <p>25 the background epidemiology and the biology of particular</p>	<p>1 recommendations or what statements are made to the public</p> <p>2 from that.</p> <p>3 (Exhibit No. 4 marked</p> <p>4 for identification.)</p> <p>5</p> <p>6 Q (By Mr. Williams) Let me have you take a look at what</p> <p>7 we've marked as Exhibit No. 4, which is a copy of this</p> <p>8 report that you provided a link to in your report at Page</p> <p>9 5.</p> <p>10 Page 5 of your report in this case, Exhibit No. 2--</p> <p>11 Dr. McTiernan, can I have your attention?</p> <p>12 A Yes.</p> <p>13 Q In the report that you wrote for this case at Page No. 5,</p> <p>14 you provided a link.</p> <p>15 Do you see that?</p> <p>16 A Yes.</p> <p>17 Q That link is to a report that you are holding in your</p> <p>18 hand, which is a 2014 ovarian cancer report, "Food,</p> <p>19 nutrition, physical activity, and prevention of ovarian</p> <p>20 cancer" that was prepared by the World Cancer Research</p> <p>21 Fund, right?</p> <p>22 A Correct.</p> <p>23 Q In the bottom right-hand corner of the page do you see</p> <p>24 there's a logo for something called the Continuous Update</p> <p>25 Project?</p>

<p style="text-align: right;">Page 70</p> <p>1 A Yes.</p> <p>2 Q That is the "CUP" for short?</p> <p>3 A Yes.</p> <p>4 Q You helped to oversee the CUP as part of its expert panel, true?</p> <p>5</p> <p>6 A I'm on an advisory committee for this project.</p> <p>7 Q Take a look at Page 20 of Exhibit No. 4-- actually, Page 19, the acknowledgments section.</p> <p>8</p> <p>9 Do you have that in front of you?</p> <p>10 A Yes.</p> <p>11 Q And that lists the panel members, correct?</p> <p>12 A Correct.</p> <p>13 Q And amongst the ten panelists, you are listed, right?</p> <p>14 A Yes.</p> <p>15 Q And the chair is Alan Jackson from the University of Southampton in Southampton, UK, right?</p> <p>16</p> <p>17 A Correct.</p> <p>18 Q You are still on the CUP panel today, are you?</p> <p>19 A It's not clear.</p> <p>20 I am advising on survivorship issues.</p> <p>21 It's not clear if this panel will continue.</p> <p>22 My term on it finished very recently, and we are renegotiating who is going to be on it and what it's going to look like for the future.</p> <p>23</p> <p>24</p> <p>25 Q In 2018--</p>	<p style="text-align: right;">Page 72</p> <p>1 convincing cause of ovarian cancer; is that true?</p> <p>2 A Can you point to where you see this?</p> <p>3 Q Page 5.</p> <p>4 I will direct your attention to the bottom of the page.</p> <p>5</p> <p>6 It says, "The CUP panel judges as follows," right?</p> <p>7 A Yes.</p> <p>8 Q And it says the CUP panel-- that's the panel that you sit on, right?</p> <p>9</p> <p>10 A Yes.</p> <p>11 Q That isn't the people who write it and that isn't the people who review the science. That's you, right?</p> <p>12</p> <p>13 A Correct.</p> <p>14 Q And it says that "The evidence that developmental factors leading to greater linear growth (marked by adult attained height) are a cause of ovarian cancer is convincing."</p> <p>15</p> <p>16</p> <p>17</p> <p>18 That's what the panel wrote, correct, or recommended?</p> <p>19</p> <p>20 A That's correct.</p> <p>21 Q Strike that.</p> <p>22 That's what the panel "judged," is the word that's used, correct?</p> <p>23</p> <p>24 A Correct.</p> <p>25 Q Is that another way of saying that factors that make some</p>
<p style="text-align: right;">Page 71</p> <p>1 A I was a part of it, yes--</p> <p>2 Q You need to let me finish.</p> <p>3 In 2018 you were a part of the panel, correct?</p> <p>4 A Correct.</p> <p>5 Q Let's take a look at Page 1 of Exhibit No. 4, which describes the mission with reference to the World Cancer Research Fund Global Network.</p> <p>6</p> <p>7</p> <p>8 It says, "Our mission: Today the World Cancer Research Fund Global Network continues," and it mentions funding, interpreting the accumulated scientific literature in the field, and educating people about choices, correct?</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13 A Correct.</p> <p>14 Q And then at the bottom of Page 1 it references the World Cancer Research Fund Global Network, and in that paragraph it references, among others, the American Institute for Cancer Research, which is the AICR, right?</p> <p>15</p> <p>16</p> <p>17</p> <p>18 A Yes.</p> <p>19 Q And on the first-- the cover page of this document, you see the AICR is referenced up at the top with the World Cancer Research Fund, right?</p> <p>20</p> <p>21</p> <p>22 A Yes.</p> <p>23 Q As a member of the panel, you concluded that developmental factors leading to greater linear growth, which is marked by adult-attained height, are a</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 73</p> <p>1 people taller than others cause ovarian cancer?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: This panel did not do a full causal analysis.</p> <p>4</p> <p>5 It does-- its purpose is quite different from the purpose of the report I prepared on talcum powder products and ovarian cancer risk.</p> <p>6</p> <p>7</p> <p>8 The purpose is not to establish causality but rather to come up with guidelines for those variables that can be interpreted into-- can be interpreted into guidelines.</p> <p>9</p> <p>10</p> <p>11 There is a set of information on how these different categories are formed, for convincing, probable associations, and then later what can be done for that, what kind of recommendations can be made to the public.</p> <p>12</p> <p>13</p> <p>14 MR. WILLIAMS: Move to strike that as nonresponsive, Doctor, if we were in court, and I will do that now for the record.</p> <p>15</p> <p>16</p> <p>17</p> <p>18 Q (By Mr. Williams) I would like to ask you to answer my question.</p> <p>19</p> <p>20 My question is whether that first paragraph there, under the "CUP panel judges as follows," is that paragraph another way of saying that factors that make some people taller than others cause ovarian cancer?</p> <p>21</p> <p>22</p> <p>23</p> <p>24 MS. PARFITT: Objection; form, asked and answered.</p> <p>25</p>

<p style="text-align: right;">Page 74</p> <p>1 THE WITNESS: So I still want to</p> <p>2 under-- state that we didn't do a full causal analysis,</p> <p>3 but there is a statement here that says these are</p> <p>4 causes-- the panel considers the strength strong enough</p> <p>5 that adult height and body fatness are causes of ovarian</p> <p>6 cancer.</p> <p>7 Q (By Mr. Williams) Does "greater linear growth" mean</p> <p>8 height?</p> <p>9 A It may not mean-- so this particular variable is never</p> <p>10 measured.</p> <p>11 You don't have the data in a population to look at</p> <p>12 linear growth over time, and so they were looking at just</p> <p>13 by adult height.</p> <p>14 Because adult height can be-- have so many variables</p> <p>15 associated with it -- genetic, nutrition -- they didn't</p> <p>16 want to assume that it's only genetic association that is</p> <p>17 driving the risk of cancer, so that's why they're talking</p> <p>18 about growth, but it's a difficult variable because you</p> <p>19 can't tell which cause the eventual adult height and</p> <p>20 which of those parts are associated with ovarian cancer</p> <p>21 or any cancer.</p> <p>22 Q You keep saying "they"-- saying "they" in your answers.</p> <p>23 This is you. This is the CUP panel that made that</p> <p>24 judgment that is set forth in Paragraph No. 1, true or</p> <p>25 not true?</p>	<p style="text-align: right;">Page 76</p> <p>1 No. 4, was not exclusively related to diet and exercise,</p> <p>2 was it?</p> <p>3 A I believe it was.</p> <p>4 Q Let me see if I can help you there.</p> <p>5 You consider causes of ovarian cancer other than</p> <p>6 those relating to diet and exercise, true?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 THE WITNESS: From my knowledge the</p> <p>9 meta-analysis work was focused on nutrition variables,</p> <p>10 physical activity variables, and obesity-related</p> <p>11 variables, all because they are related to nutrition, as</p> <p>12 well as lactation because that's also a nutrition-related</p> <p>13 variable.</p> <p>14 Q (By Mr. Williams) Your panel wrote about causes of</p> <p>15 ovarian cancer other than those relating to diet and</p> <p>16 exercise, true?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 THE WITNESS: The panel did not-- I</p> <p>19 will have to look and see what they said about other</p> <p>20 causes, but the panel was focused on, in terms of the</p> <p>21 meta-analysis, the new data that they are presenting, is</p> <p>22 all related to nutrition, physical activity, and diet.</p> <p>23 Q (By Mr. Williams) Whether it's new data-- strike that.</p> <p>24 First of all, Doctor, you said "they" again.</p> <p>25 You mean you, you mean "our panel," correct?</p>
<p style="text-align: right;">Page 75</p> <p>1 A Correct, it was the panel.</p> <p>2 MS. PARFITT: Objection.</p> <p>3 Q (By Mr. Williams) The second paragraph says, "Greater</p> <p>4 body fatness, which the panel interprets to be marked by</p> <p>5 the body mass index, is probably a cause of ovarian</p> <p>6 cancer."</p> <p>7 Do you see that?</p> <p>8 A Yes.</p> <p>9 Q That was a judgment made by the panel upon which you sit,</p> <p>10 correct?</p> <p>11 A Correct.</p> <p>12 Q The third paragraph says, "The evidence suggesting that</p> <p>13 lactation protects against ovarian cancer is limited."</p> <p>14 That too was a panel judgment made by the panel upon</p> <p>15 which you sit, right?</p> <p>16 A Correct.</p> <p>17 Q The panel that you were on, at least as of 2018, was</p> <p>18 primarily looking at causes of ovarian cancer related to</p> <p>19 diet and exercise; is that accurate?</p> <p>20 A The panel only looks at those related variables.</p> <p>21 Lactation is included because it has some</p> <p>22 nutritional components, but all of the variables that</p> <p>23 this organization looks at and-- that's their mission.</p> <p>24 The nutrition-related variables is what they look at.</p> <p>25 Q But the panel report that is in front of you, Exhibit</p>	<p style="text-align: right;">Page 77</p> <p>1 A When I say "they," the meta-analysis, I did not do the</p> <p>2 meta-analysis.</p> <p>3 the meta-analysis was done by Imperial College.</p> <p>4 The meta-analysis was contracted by World Cancer</p> <p>5 Research Fund to Imperial College to do those</p> <p>6 meta-analysis.</p> <p>7 What the panel did is-- we're a group of scientists.</p> <p>8 We review those data once they're done.</p> <p>9 Q You review the data once it's done?</p> <p>10 A Once it's done.</p> <p>11 Q And you make recommendations as a panel member, correct?</p> <p>12 A We make judgments.</p> <p>13 The recommendations are a combination of us and</p> <p>14 WCRF.</p> <p>15 Q One of the judgments that is-- strike that.</p> <p>16 On Page 7 of the document, Exhibit No. 4, there is a</p> <p>17 listing entitled, "Other established causes."</p> <p>18 Do you see that?</p> <p>19 A Yes.</p> <p>20 Q And those are established causes of ovarian cancer,</p> <p>21 correct?</p> <p>22 A Correct.</p> <p>23 Q That paragraph--</p> <p>24 A Sorry, say that again.</p> <p>25 Q The other established causes that are being referred to</p>

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<p>1 here are established causes of ovarian cancer, correct?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 Q (By Mr. Williams) Do you understand my question?</p> <p>4 A I do.</p> <p>5 What I'm trying to say-- what I want to say here is</p> <p>6 there was no systematic review done here.</p> <p>7 This was information that was largely taken from the</p> <p>8 second expert report and repeated here, so this was data</p> <p>9 from 2007-- information from 2007, and there was no--</p> <p>10 except for lactation, among all these variables there was</p> <p>11 no new review done by the panel.</p> <p>12 This was the knowledge at the time of the second</p> <p>13 annual report, 2007, of variables that are-- that the</p> <p>14 2007 expert panel thought were related to ovarian cancer.</p> <p>15 Q Hold on, Doctor.</p> <p>16 In 2014, which is the date of this document, you</p> <p>17 were sitting on the World Cancer Research Fund's panel,</p> <p>18 correct?</p> <p>19 A Correct.</p> <p>20 Q The panel reviews the results of the epidemiological</p> <p>21 analysis that is done by others, correct?</p> <p>22 A Reviews the data, the meta-analysis from the nutrition</p> <p>23 variables, yes.</p> <p>24 Q And then it sets forth judgments and it writes the text</p> <p>25 that appears in this document, correct?</p>	<p>1 probable cause of ovarian cancer, true?</p> <p>2 A If you're talking about this paragraph, I don't see it</p> <p>3 there.</p> <p>4 Q And this paragraph does not describe talc as a risk</p> <p>5 factor for ovarian cancer, such as hormone replacement</p> <p>6 therapy, correct?</p> <p>7 A Talcum powder products are not mentioned there, correct.</p> <p>8 Q This 2004 CUP report-- strike that.</p> <p>9 Did this 2014 CUP report come out before or after</p> <p>10 Plaintiffs' counsel hired you as an expert in this case?</p> <p>11 A This came out before I was hired.</p> <p>12 This was a 2014 report.</p> <p>13 We may have downloaded this recently.</p> <p>14 The way these reports work is the work for the</p> <p>15 meta-analysis is done, and then the panel reviews the</p> <p>16 data, and then a report is drafted and published online</p> <p>17 at that time, so if it says, "2014," then it would have</p> <p>18 been online in 2014, would have been public then.</p> <p>19 Q And there have been reports that have been prepared by</p> <p>20 the World Cancer Research Fund and the American Institute</p> <p>21 for Cancer Research since this 2014 report, right?</p> <p>22 MS. PARFITT: Objection to the form.</p> <p>23 THE WITNESS: Different cancers would</p> <p>24 have been since then.</p> <p>25 I don't have memorized exactly when the different</p>
Page 79	Page 81
<p>1 A The panel did not write this text.</p> <p>2 The panel-- the World Cancer Research Fund wrote</p> <p>3 this text.</p> <p>4 Q Are you disavowing Page 7, third paragraph, "Other</p> <p>5 established causes," that's set forth other established</p> <p>6 causes for ovarian cancer?</p> <p>7 MS. PARFITT: Objection; form,</p> <p>8 misstates her testimony.</p> <p>9 THE WITNESS: The question was am I</p> <p>10 disavowing-- I am not disavowing.</p> <p>11 I am saying it was not written by our panel.</p> <p>12 We reviewed it. We had opportunity to have input,</p> <p>13 but we were not the final authors of this section.</p> <p>14 Q (By Mr. Williams) When you read the section, did you</p> <p>15 say, "Wait a minute, you haven't included anything in</p> <p>16 here about talc causing ovarian cancer"?</p> <p>17 Did you tell anybody that?</p> <p>18 A I don't recall doing that.</p> <p>19 At the time I had not done a full analysis of</p> <p>20 ovarian cancer risk factors.</p> <p>21 Q When you say that you don't recall doing it, are you</p> <p>22 saying it might have happened, it might not have</p> <p>23 happened, or are you saying that it did not happen?</p> <p>24 A It did not happen.</p> <p>25 Q This document does not include talc as a cause or</p>	<p>1 years came out.</p> <p>2 In-- last spring, and I think it was 2018, but it</p> <p>3 could have been 2017, there was a final report of WCRF</p> <p>4 that included all of these reports, but this was not</p> <p>5 changed at that time.</p> <p>6 The final report that came out was more of a global</p> <p>7 summary and global nutrition recommendations, but these</p> <p>8 all-- that's why it's called the Continuous Update</p> <p>9 Project, because these things are updated at various</p> <p>10 points and then they become part of that final report,</p> <p>11 2017, 2018.</p> <p>12 This is why I was-- I said that the panel may be</p> <p>13 reconstituted, because we finished one set of cancers,</p> <p>14 one set of reports.</p> <p>15 Q (By Mr. Williams) The whole idea of the CUP reports is</p> <p>16 that they get updated continuously, right?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 THE WITNESS: The ovarian cancer was</p> <p>19 not updated after 2014.</p> <p>20 Is that your question?</p> <p>21 Q (By Mr. Williams) Are you sure about that?</p> <p>22 A From my knowledge it was not updated.</p> <p>23 Q Take a look at Page 2 of Exhibit No. 4 that you have.</p> <p>24 At the top of Page 2 it says, "Please cite the</p> <p>25 report as follows," and it gives instructions about how</p>



<p style="text-align: right;">Page 82</p> <p>1 the report should be cited, correct?</p> <p>2 A Yes.</p> <p>3 Q It's accurate to say that the expectation of the</p> <p>4 publication of this report is that it may be cited by</p> <p>5 others, right?</p> <p>6 A Yes.</p> <p>7 Q That's why you have this at the top of Page No. 2,</p> <p>8 correct?</p> <p>9 A Yes.</p> <p>10 Q Let me show you another document, which we'll mark as</p> <p>11 Exhibit No. 5.</p> <p>12 (Exhibit No. 5 marked</p> <p>13 for identification.)</p> <p>14</p> <p>15 Q (By Mr. Williams) Exhibit No. 5, for the record, is a</p> <p>16 multi-page document that says, "Diet, nutrition, physical</p> <p>17 activity and ovarian cancer - revised 2018" on the cover</p> <p>18 page.</p> <p>19 Do you see that?</p> <p>20 A Yes.</p> <p>21 Q The CUP expert panel that you sat on through 2018 issued</p> <p>22 this collection of reports entitled, "Diet, nutrition,</p> <p>23 physical activity and cancer, a global perspective,"</p> <p>24 right?</p> <p>25 A Yes.</p>	<p style="text-align: right;">Page 84</p> <p>1 A Correct.</p> <p>2 Q The CUP expert panel that you sat on through last year is</p> <p>3 in fact the body that issues these reports, like Exhibit</p> <p>4 No. 5, correct?</p> <p>5 A Correct.</p> <p>6 Q Now let me have you look at Exhibit No. 5, which is the</p> <p>7 2018 CUP report.</p> <p>8 I will just quickly refer you to Page 4.</p> <p>9 On Page 4 there's a heading that says, "Our</p> <p>10 Continuous Update Project, CUP"-- do you see that?</p> <p>11 A Yes.</p> <p>12 MS. PARFITT: Give her just one</p> <p>13 moment.</p> <p>14 Q (By Mr. Williams) And then the second paragraph says,</p> <p>15 "An independent panel of experts carries out ongoing</p> <p>16 evaluations of this evidence, and their findings form the</p> <p>17 basis of the WCRF network's cancer prevention</p> <p>18 recommendations."</p> <p>19 Do you see that?</p> <p>20 A Yes.</p> <p>21 Q That's referring to your panel, correct?</p> <p>22 A Yes.</p> <p>23 Q And if you look at the back of this document that's on</p> <p>24 Page 21, in the acknowledgments section, it lists the</p> <p>25 panel members.</p>
<p style="text-align: right;">Page 83</p> <p>1 Q This is the most recent version of the Continuous Update</p> <p>2 Project report that we were just looking at, right?</p> <p>3 A Yes.</p> <p>4 Q Let me show you another document, which is-- we'll mark</p> <p>5 as Exhibit No. 6.</p> <p>6 (Exhibit No. 6 marked</p> <p>7 for identification.)</p> <p>8</p> <p>9 Q (By Mr. Williams) I will ask you to keep Exhibit No. 5</p> <p>10 nearby.</p> <p>11 Exhibit No. 6, I will represent to you, is the CUP</p> <p>12 panel web page, which we printed out on January 7th,</p> <p>13 2019.</p> <p>14 Are you pictured in the picture there?</p> <p>15 A Yes.</p> <p>16 Q Is that you five people over from the right?</p> <p>17 A Yes.</p> <p>18 Q Above the photo that you appear in, do you see where it</p> <p>19 says, "In 2018 the expert panel, chaired by Professor</p> <p>20 Alan Jackson, issued our latest cancer prevention</p> <p>21 recommendations as part of the World Cancer Research</p> <p>22 Fund/American Institute for Cancer Research third expert</p> <p>23 report, 'Diet, nutrition, physical activity and cancer: a</p> <p>24 global perspective."</p> <p>25 That's what it says, correct?</p>	<p style="text-align: right;">Page 85</p> <p>1 I've counted. There are now nine panelists as of</p> <p>2 2018, and you are listed as one, correct?</p> <p>3 A You are looking at-- sorry, which?</p> <p>4 Q Page 21 of Exhibit No. 5.</p> <p>5 Do you see it listed there on Page 21?</p> <p>6 A Yes.</p> <p>7 Q Now, please go back to Page 6 of Exhibit No. 5, the 2018</p> <p>8 report of the World Cancer Research Fund.</p> <p>9 Under the box "Summary of panel judgments," do you</p> <p>10 see there that the same conclusions that were set forth</p> <p>11 in the 2014 report concerning the panel judgments are set</p> <p>12 forth?</p> <p>13 A So you are talking about this table--</p> <p>14 Q If you look in the lower left-hand corner of the page, it</p> <p>15 has Page No. 6.</p> <p>16 Are you looking at the 2018--</p> <p>17 A It says, "Summary of panel judgments."</p> <p>18 Q Correct, and do you see the box that's underneath there</p> <p>19 with subheadings?</p> <p>20 A Yeah.</p> <p>21 One thing to point out is that this table, which is</p> <p>22 the summary-- so you are in Exhibit No. 5 ? It says,</p> <p>23 "2014," so it's the exact same as this 2014 report.</p> <p>24 Q Ma'am, I am not even looking at that page.</p> <p>25 A Okay.</p>



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<p>1 Q I am asking you to look at Page 6.</p> <p>2 A Page 6.</p> <p>3 Q Which says, "The summary of the panel judgments."</p> <p>4 A Okay.</p> <p>5 Q In that summary of the panel judgments it sets forth the</p> <p>6 same conclusions that were contained in the 2014 report</p> <p>7 regarding linear growth, body fatness, and lactation,</p> <p>8 correct?</p> <p>9 A That's correct.</p> <p>10 Q There's no reference to talcum powder here either,</p> <p>11 correct?</p> <p>12 A That's correct.</p> <p>13 Q As of 2018 you had been retained as an expert by the</p> <p>14 plaintiffs' lawyers in this litigation; is that correct?</p> <p>15 MS. PARFITT: Objection; form.</p> <p>16 THE WITNESS: The summaries are</p> <p>17 regarding the data analyzed by WCRF on nutrition</p> <p>18 variables.</p> <p>19 They do not consider-- they do not do systematic</p> <p>20 reviews for other ovarian cancer risk factors, only</p> <p>21 nutrition variables.</p> <p>22 Q (By Mr. Williams) Let me ask you to go to Page 3.</p> <p>23 Again in your last answer you said "they."</p> <p>24 You are a panelist for this organization, correct?</p> <p>25 A Yes, I am a panelist, but I don't-- I am not in a</p>	<p>1 in 2018, which is after you had been retained by</p> <p>2 plaintiff lawyers to opine on whether or not talc could</p> <p>3 cause ovarian cancer, true or not true?</p> <p>4 MS. PARFITT: Objection; form, asked</p> <p>5 and answered.</p> <p>6 THE WITNESS: I want to be able to</p> <p>7 answer this to try to make it more clear.</p> <p>8 If you see on the cover, it says, "2014."</p> <p>9 This is the 2014 report that was added to all of the</p> <p>10 other reports.</p> <p>11 Some were developed in 2011, some in 2017.</p> <p>12 We did not redo the meta-analyses. We did not redo</p> <p>13 the entire report.</p> <p>14 They were added together.</p> <p>15 The World Cancer Research Fund for the first two</p> <p>16 reports did all of the work at one time and came up with</p> <p>17 books, so the most recent one was 2007.</p> <p>18 This time they decided to do reports on a rolling</p> <p>19 basis. That's why Ovarian came out in 2014, but that</p> <p>20 their final-- when they put it all together, they</p> <p>21 celebrate, come out with big systematic-- sorry, summary</p> <p>22 guidelines for the public for preventing cancer-related</p> <p>23 nutrition, physical activity, things that people can do--</p> <p>24 that was all added together in 2018, but this ovarian</p> <p>25 report was from 2014.</p>
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<p>1 position to choose what WCRF decides to contract out for</p> <p>2 analyses.</p> <p>3 They contract with the Imperial College of what the</p> <p>4 focus is going to be: nutrition, physical activity, diet.</p> <p>5 It's my-- I have the ability to refuse to be on the</p> <p>6 panel, to decline if I don't want to be involved with</p> <p>7 nutrition, physical activity, and obesity research</p> <p>8 because that's the mission. The mission are those</p> <p>9 variables, not to do systematic reviews on other risk</p> <p>10 factors.</p> <p>11 We don't do anything on cigarette smoking or other</p> <p>12 types of carcinogens, for example.</p> <p>13 We only do nutrition, physical activity,</p> <p>14 obesity-related variables.</p> <p>15 Q To be clear, this CUP update on ovarian cancer came out</p> <p>16 in 2018, which is after you were retained by plaintiff</p> <p>17 lawyers to opine on whether or not talc could cause</p> <p>18 ovarian cancer.</p> <p>19 Is that true or not true?</p> <p>20 MS. PARFITT: Objection; form, asked</p> <p>21 and answered.</p> <p>22 Q (By Mr. Williams) I am looking for a temporal answer.</p> <p>23 This--</p> <p>24 MS. PARFITT: Same objection.</p> <p>25 Q (By Mr. Williams) This update on ovarian cancer came out</p>	<p>1 MR. WILLIAMS: I will move to strike</p> <p>2 that as nonresponsive.</p> <p>3 Q (By Mr. Williams) Dr. McTiernan, on the first page of</p> <p>4 this document it says it was revised in 2018.</p> <p>5 This document that's in front of you now was</p> <p>6 published in 2018, wasn't it?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 She has been asked and answered it.</p> <p>9 You have limited time, Mr. Williams, so I suggest</p> <p>10 you listen to her answer.</p> <p>11 Q (By Mr. Williams) This document was published in 2018,</p> <p>12 yes or no?</p> <p>13 MS. PARFITT: Objection; form, asked</p> <p>14 and answered.</p> <p>15 THE WITNESS: This document was</p> <p>16 published along with all of the other documents, but the</p> <p>17 document was prepared in 2014.</p> <p>18 It's a report in 2014.</p> <p>19 Q (By Mr. Williams) What year was this document published?</p> <p>20 MS. PARFITT: The document speaks for</p> <p>21 itself. Objection; form.</p> <p>22 THE WITNESS: It says, "Revised 2018."</p> <p>23 Q (By Mr. Williams) 2018 was after you were retained by</p> <p>24 Plaintiffs' counsel, correct?</p> <p>25 MS. PARFITT: Objection; form,</p>

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<p>1 mischaracterizes her testimony.</p> <p>2 Q (By Mr. Williams) You may answer, Doctor.</p> <p>3 MS. PARFITT: Objection; form.</p> <p>4 Answer as best you can.</p> <p>5 THE WITNESS: Yes, 2018 is after I was</p> <p>6 retained.</p> <p>7 Q (By Mr. Williams) It was a couple years after you had</p> <p>8 been retained, right?</p> <p>9 A That's correct.</p> <p>10 Q Could you list for me all of the members of the panel who</p> <p>11 served with you on the World Cancer Research Fund whom</p> <p>12 you told, "We need to update this to state that talc,</p> <p>13 which is something that people can use or not use, is</p> <p>14 something that they should not use because it causes</p> <p>15 ovarian cancer"?</p> <p>16 List for me the people who are listed on Page 21, as</p> <p>17 fellow panel members, all of the people that you have</p> <p>18 told that.</p> <p>19 A I didn't talk with others about other risk factors for</p> <p>20 ovarian cancer because we were using the same report</p> <p>21 unchanged from 2014.</p> <p>22 Q Is the answer that there's no one?</p> <p>23 MS. PARFITT: Objection; misstates her</p> <p>24 testimony.</p> <p>25 Q (By Mr. Williams) Is the answer that there is no one</p>	<p>1 This says, "Our cancer prevention recommendations."</p> <p>2 When it says "our" there, that refers to the panel</p> <p>3 on which you sat in 2018, correct?</p> <p>4 A This is correct.</p> <p>5 This is a separate document.</p> <p>6 It must have been from the ovarian report because</p> <p>7 this is-- there are separate recommendations based on all</p> <p>8 of the cancers.</p> <p>9 Q The panel does not recommend limiting or stopping the use</p> <p>10 of talcum powder, correct?</p> <p>11 A The panel did not look at all potential carcinogens.</p> <p>12 The panel looked and developed recommendations based</p> <p>13 on nutrition, physical activity, and obesity-related</p> <p>14 variables.</p> <p>15 Q Is the answer that it does not list talc?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 THE WITNESS: It does not list talc,</p> <p>18 but it doesn't list other carcinogens as well.</p> <p>19 Q (By Mr. Williams) Please turn to Page 8.</p> <p>20 I am referring to Page 8 of the 2018 CUP report.</p> <p>21 I will direct your attention to Section 4 at the top</p> <p>22 that says, "Other established causes."</p> <p>23 Do you see that?</p> <p>24 A Yes.</p> <p>25 Q Not bearing children is listed as something that may be</p>
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<p>1 there?</p> <p>2 MS. PARFITT: Objection; form,</p> <p>3 misstates her testimony.</p> <p>4 Q (By Mr. Williams) You may answer.</p> <p>5 A Correct.</p> <p>6 MS. PARFITT: You may answer.</p> <p>7 Q (By Mr. Williams) Is the answer correct?</p> <p>8 A Correct.</p> <p>9 MS. PARFITT: Objection.</p> <p>10 MR. WILLIAMS: Counsel, I am entitled</p> <p>11 to an answer to the question.</p> <p>12 MS. PARFITT: You can, and I'm</p> <p>13 entitled to object to the form.</p> <p>14 MR. WILLIAMS: But you are objecting</p> <p>15 over her answer.</p> <p>16 MS. PARFITT: No, I am objecting-- she</p> <p>17 is answering quite quickly. I am trying to object before</p> <p>18 she answers, but after you.</p> <p>19 MR. WILLIAMS: Fair enough.</p> <p>20 MS. PARFITT: Thanks.</p> <p>21 Q (By Mr. Williams) Please turn to the second-to-last page</p> <p>22 of this 2018 CUP report, which is entitled, "Our cancer</p> <p>23 prevention recommendations."</p> <p>24 It is a purple page. It is the inside cover of the</p> <p>25 pamphlet.</p>	<p>1 seen as a cause of ovarian cancer, correct?</p> <p>2 A Correct.</p> <p>3 Q Early menarche or age of first period is listed as</p> <p>4 something that your panel concluded may be seen as a</p> <p>5 cause of ovarian cancer, true?</p> <p>6 A It wasn't a panel conclusion. We weren't asked to judge</p> <p>7 data.</p> <p>8 This was written up as a background for other</p> <p>9 potential causes.</p> <p>10 There were no data that was reviewed by the panel.</p> <p>11 Q The heading is, "Other established causes," right?</p> <p>12 A Right.</p> <p>13 WCRF prefers to use that language. I'm not sure I</p> <p>14 would have used that.</p> <p>15 Q Talc is not listed as an established cause, correct?</p> <p>16 A It is not.</p> <p>17 It looks like the paragraph was unchanged from 2014.</p> <p>18 It was not updated.</p> <p>19 This report, from my knowledge, is the same in 2014</p> <p>20 as this-- as what's called "Revised," but I believe it's</p> <p>21 the same report.</p> <p>22 Q Did you, as a member of this expert panel, conclude that</p> <p>23 talc could be seen as a cause of ovarian cancer?</p> <p>24 A This expert panel didn't consider talc.</p> <p>25 Q Is the answer "no?"</p>

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<p>1 MS. PARFITT: Objection; form--</p> <p>2 THE WITNESS: All I can say is we</p> <p>3 didn't consider-- we didn't review the literature. We</p> <p>4 didn't do-- review any of these other variables in</p> <p>5 totality.</p> <p>6 Q (By Mr. Williams) Is there any reason why you don't do</p> <p>7 that?</p> <p>8 A We were tasked at looking at nutrition, physical</p> <p>9 activity, and obesity-related variables.</p> <p>10 Q Tasked by whom?</p> <p>11 A By WCRF, World Cancer Research Fund.</p> <p>12 Q Did the World Cancer Research Fund say that you could not</p> <p>13 look into talc?</p> <p>14 MS. PARFITT: Objection; form.</p> <p>15 THE WITNESS: They did-- in our</p> <p>16 personal lives, that we could look into any variable you</p> <p>17 wanted to, but for this purpose of this panel, we were</p> <p>18 only looking at and evaluating the meta-analysis, which</p> <p>19 was focused on physical activity, diet, and nutrition</p> <p>20 variables.</p> <p>21 Q (By Mr. Williams) Let me ask you to turn to Page 7 of</p> <p>22 the CUP report.</p> <p>23 A Which one?</p> <p>24 Q Page 7 of the 2018 report, Exhibit No. 5.</p> <p>25 A Okay.</p>	<p>1 cancers.</p> <p>2 "Spontaneous" means something else caused it.</p> <p>3 Q However you define "spontaneous," do you agree that most</p> <p>4 ovarian cancers occur spontaneously?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: I agree that most-- I</p> <p>7 would not use that word myself because it can be</p> <p>8 misconstrued by nonscientists.</p> <p>9 "Spontaneous" means "nongenetically inherited," so I</p> <p>10 would say environmental, that most cancers-- most ovarian</p> <p>11 cancers are caused by something in the environment, some</p> <p>12 exposure.</p> <p>13 Q (By Mr. Williams) Did you tell someone to take out the</p> <p>14 word "spontaneously"?</p> <p>15 A I don't recall.</p> <p>16 We did have an opportunity in 2014 to edit these</p> <p>17 various reports.</p> <p>18 None of us had final say on exactly what came out of</p> <p>19 the report.</p> <p>20 We did go through a process of editing.</p> <p>21 Q When you had the opportunity to edit the report in 2014,</p> <p>22 did you ask someone to take out the word "spontaneously"?</p> <p>23 A I don't recall.</p> <p>24 Q When you say you don't recall, are you saying it may have</p> <p>25 happened, it may not have happened?</p>
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<p>1 Q Do you see the heading that says, "Pathogenesis"?</p> <p>2 A Yes.</p> <p>3 Q Do you see where in the second paragraph the panel</p> <p>4 concluded that the-- quote, "Most ovarian cancers occur</p> <p>5 spontaneously, although five to ten percent of cases</p> <p>6 develop due to a genetic disposition," Closed quote?</p> <p>7 Do you see that?</p> <p>8 A I see that, and above that I see that "The epithelial</p> <p>9 cells are subjected to a unique pro-inflammatory</p> <p>10 microenvironment, which can increase the rate of DNA</p> <p>11 damage, thus affecting cancer risk."</p> <p>12 In this case the word "spontaneous" just means "as</p> <p>13 opposed to genetics."</p> <p>14 Spontaneous cancers mean they can be caused by</p> <p>15 anything else, including environment, but not solely due</p> <p>16 to an inherited genetic predisposition.</p> <p>17 Q Do you agree that most ovarian cancers occur</p> <p>18 spontaneously?</p> <p>19 A I believe most are caused by environmental causes as for</p> <p>20 many other cancers.</p> <p>21 I am using the word "spontaneous." I mean "non</p> <p>22 solely genetic."</p> <p>23 Cancer is a genetic disease, but the familial</p> <p>24 genetic-inherited cancers account for only about five to</p> <p>25 ten percent of ovarian cancers, similar to many other</p>	<p>1 A It may have happened, it may not.</p> <p>2 I apologize, I don't recall.</p> <p>3 Q And after you make such a recommendation as a panelist,</p> <p>4 who decides what gets put in?</p> <p>5 A The World Cancer Research Fund. The scientific officers</p> <p>6 would decide.</p> <p>7 Q They would listen to the input and then decide one way or</p> <p>8 the other?</p> <p>9 A Yes.</p> <p>10 Q In 2014 the Gertig 2000 and Terry 2013 studies on talc,</p> <p>11 that you reviewed in 2016, had already been published,</p> <p>12 correct?</p> <p>13 A I am hesitating because I don't remember when this exact</p> <p>14 writing was.</p> <p>15 If it's a 2014 report, that's when it came out.</p> <p>16 It could have been being written within 2013, so at</p> <p>17 the time I was not doing research on all of the variables</p> <p>18 related to ovarian cancer, so I can't say what was</p> <p>19 published at that time.</p> <p>20 Q 2014 is after 2013, correct?</p> <p>21 A That's correct.</p> <p>22 Q If Gertig was published in 2000, Gertig would have been</p> <p>23 published prior to the time that this exhibit, the 2014</p> <p>24 version of this exhibit, was published, correct?</p> <p>25 A Published but perhaps not when it was prepared, that's</p>

<p style="text-align: right;">Page 98</p> <p>1 what I'm saying.</p> <p>2 Q If the Terry study was published in 2013, it would have</p> <p>3 been published prior to the time that the 2014 version of</p> <p>4 the World Cancer Research Fund would have been published,</p> <p>5 correct?</p> <p>6 A It would have been published prior to publication, not</p> <p>7 necessarily prior to report preparation.</p> <p>8 Q Have you ever been on the World Cancer Research Fund web</p> <p>9 page?</p> <p>10 A Yes, I have.</p> <p>11 Q Let me show you what we've marked as Exhibit No. 7 or</p> <p>12 what we will mark as Exhibit No. 7 to your deposition.</p> <p>13 (Exhibit No. 7 marked</p> <p>14 for identification.)</p> <p>15</p> <p>16 Q (By Mr. Williams) Exhibit No. 7 is the World Cancer</p> <p>17 Research Fund web page.</p> <p>18 We printed this out as of January 8th, 2019.</p> <p>19 It's a five-page document, and the portion that we</p> <p>20 printed out is "Myths and controversies about what causes</p> <p>21 cancer."</p> <p>22 Do you see that?</p> <p>23 A Yes, I do.</p> <p>24 Q There is only one World Cancer Research Fund, to your</p> <p>25 knowledge, correct?</p>	<p style="text-align: right;">Page 100</p> <p>1 if you are trying to get to the World Cancer Research</p> <p>2 Fund website.</p> <p>3 Will you accept that representation, ma'am?</p> <p>4 A It looks like it comes from their website.</p> <p>5 I am not clear on who developed this or-- it</p> <p>6 certainly didn't have oversight by our committee.</p> <p>7 Our committee was tasked at looking at the data from</p> <p>8 the meta-analysis and systematic review.</p> <p>9 None of these variables-- none of the variables</p> <p>10 here, except perhaps coffee, were considered by my panel.</p> <p>11 My panel does not oversee all World Cancer Research</p> <p>12 Fund. There are other groups that oversee them.</p> <p>13 I do not.</p> <p>14 I oversee-- sorry, I participate on one panel that</p> <p>15 focuses on nutrition, physical activity, and diet</p> <p>16 meta-analyses.</p> <p>17 Q Take a look at Page 2 of this document, which is Exhibit</p> <p>18 No. 7.</p> <p>19 At the top of the page it says, "Cosmetics and</p> <p>20 toiletries."</p> <p>21 Do you see that?</p> <p>22 A I do.</p> <p>23 Q It says, "Most studies have found no link between cancer</p> <p>24 and the chemicals used in cosmetic and toiletry products,</p> <p>25 such as moisturizers, shampoos, deodorants, and</p>
<p style="text-align: right;">Page 99</p> <p>1 A That's correct.</p> <p>2 Q The World Cancer Research Fund, the organization for whom</p> <p>3 you have served as an advisory panel member for years,</p> <p>4 tries to advise the public about potential causes for</p> <p>5 cancer, correct?</p> <p>6 MS. PARFITT: Objection; form.</p> <p>7 THE WITNESS: Their focus is on</p> <p>8 nutrition, physical activity, and obesity variables.</p> <p>9 That's what they advise on. That's what their</p> <p>10 recommendations are.</p> <p>11 Q (By Mr. Williams) The World Cancer Research Fund tries</p> <p>12 to debunk myths about what has been established as a</p> <p>13 cause of cancer, correct?</p> <p>14 MS. PARFITT: Objection; form.</p> <p>15 THE WITNESS: Before I answer that, I</p> <p>16 would like to know if this is a Blount post.</p> <p>17 If it's not-- it's not something that has come</p> <p>18 before the World Cancer Research Fund.</p> <p>19 We would never investigate or were never asked to</p> <p>20 comment on these particular issues.</p> <p>21 Q (By Mr. Williams) I will represent to you that the</p> <p>22 address that is listed at the bottom of the page, which</p> <p>23 includes</p> <p>24 www.wcrf-uk.org/uk/preventing-cancer/cancer-risk-factors-</p> <p>25 and it goes on, is, in fact, where you get-- where you go</p>	<p style="text-align: right;">Page 101</p> <p>1 toothpastes. The majority of countries have strict</p> <p>2 regulations to ensure these products are safe."</p> <p>3 Do you see that?</p> <p>4 A Yes.</p> <p>5 Q It goes on, second paragraph, "Some studies have found a</p> <p>6 link between talcum powder, talc, and ovarian cancer, but</p> <p>7 there is not enough evidence to be certain of this. Even</p> <p>8 if there were an increased risk, scientists estimate it</p> <p>9 would be small. Not smoking, followed by maintaining a</p> <p>10 healthy weight through eating a healthy diet and keeping</p> <p>11 active, are the most effective ways to reduce your cancer</p> <p>12 risk."</p> <p>13 Did I read that right?</p> <p>14 A Yes, you did.</p> <p>15 Q Do you disagree with that statement of the World Cancer</p> <p>16 Research Fund?</p> <p>17 A I do.</p> <p>18 I am surprised it's there.</p> <p>19 Q Is it accurate to say that your opinion in this case that</p> <p>20 the state of known scientific evidence establishes that</p> <p>21 perineal use of talc causes ovarian cancer conflicts with</p> <p>22 the conclusion set forth on the website of the World</p> <p>23 Cancer Research Fund that there is not enough evidence to</p> <p>24 be certain that there is a link between talcum powder use</p> <p>25 and ovarian cancer?</p>

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<p>1 MS. PARFITT: Objection; form,</p> <p>2 misstates the document.</p> <p>3 THE WITNESS: I do disagree.</p> <p>4 Q (By Mr. Williams) Your opinion in this case conflicts</p> <p>5 with the--</p> <p>6 A Yes, my opinion conflicts--</p> <p>7 Q You need to wait until I'm done, ma'am if you would.</p> <p>8 A Okay.</p> <p>9 Q Your opinion in this case, as set forth in your report,</p> <p>10 conflicts with the conclusions set forth specifically</p> <p>11 regarding talcum powder on the World Cancer Research Fund</p> <p>12 website, correct?</p> <p>13 MS. PARFITT: Objection to the form.</p> <p>14 THE WITNESS: Yes, that's correct.</p> <p>15 Q (By Mr. Williams) The American Institute for Cancer</p> <p>16 Research tries to advise the public regarding potential</p> <p>17 causes of cancer; is that right?</p> <p>18 MS. PARFITT: Objection; form,</p> <p>19 misstates her testimony.</p> <p>20 THE WITNESS: The American Institute</p> <p>21 for Cancer Research is part of the World Cancer Research</p> <p>22 Foundation, and they have the same mission, to focus on</p> <p>23 nutrition, physical activity, and obesity in relation to</p> <p>24 cancer risk and survival.</p> <p>25 Q (By Mr. Williams) Did you know that the American</p>	<p>1 A Yes.</p> <p>2 Q And the second paragraph that's listed there on Exhibit</p> <p>3 No. 8 is identical to the paragraph that we just went</p> <p>4 over in Exhibit No. 7 relating to talcum powder and</p> <p>5 ovarian cancer; is that right?</p> <p>6 A Yes, I see that.</p> <p>7 Q Is it accurate to say that your opinion in this case,</p> <p>8 that the state of known scientific evidence establishes</p> <p>9 that perineal use of talc causes ovarian cancer,</p> <p>10 conflicts with the conclusion of the American Institute</p> <p>11 for Cancer Research, that there is not enough evidence to</p> <p>12 be certain that there is a link between talc use and</p> <p>13 ovarian cancer?</p> <p>14 MS. PARFITT: Objection; form.</p> <p>15 THE WITNESS: Yes, I disagree with</p> <p>16 what they have written here.</p> <p>17 Q (By Mr. Williams) You have never told anyone from the</p> <p>18 AICR, I take it, that you disagree?</p> <p>19 MS. PARFITT: Objection; form.</p> <p>20 THE WITNESS: I did not know that they</p> <p>21 had this on their website.</p> <p>22 I think I will talk to them now.</p> <p>23 Q (By Mr. Williams) Let me direct your attention to a new</p> <p>24 document, which is an article from Hutch News that refers</p> <p>25 to you.</p>
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<p>1 Institute for Cancer Research includes a page on its</p> <p>2 website discussing whether different exposures can cause</p> <p>3 cancer?</p> <p>4 A I would have to see it, but no, I do not follow whatever</p> <p>5 page you're talking about.</p> <p>6 I don't know what you're referring to.</p> <p>7 (Exhibit No. 8 marked</p> <p>8 for identification.)</p> <p>9</p> <p>10 Q (By Mr. Williams) Let me show you what we've marked as</p> <p>11 Exhibit No. 8.</p> <p>12 Exhibit No. 8 is a three-page document, which is a</p> <p>13 printout of the website of the AICR. The address is</p> <p>14 listed at the bottom of Page 1 of Exhibit No. 8.</p> <p>15 You are familiar with the American Institute for</p> <p>16 Cancer Research?</p> <p>17 A Yes, I am.</p> <p>18 It is a part of the World Cancer Research Fund.</p> <p>19 Q I would like you to look at the first page of Exhibit</p> <p>20 No. 8.</p> <p>21 There is a listing that says, "GMOs and other hot</p> <p>22 topics," and then there are seven different topics that</p> <p>23 are set forth, the fifth of which is cosmetics and</p> <p>24 toiletries.</p> <p>25 Do you see that?</p>	<p>1 We'll mark it as Exhibit No. 9.</p> <p>2 (Exhibit No. 9 marked</p> <p>3 for identification.)</p> <p>4</p> <p>5 Q (By Mr. Williams) This is an article that was published</p> <p>6 on May 25th, 2018, correct?</p> <p>7 It's a commentary written by you?</p> <p>8 A Yes. It was edited by-- our communications department</p> <p>9 edited it, so I authored it, but they adjusted it.</p> <p>10 Q May 25, 2018 was at least a year and a half after you had</p> <p>11 been retained by plaintiffs' counsel for this engagement,</p> <p>12 correct?</p> <p>13 MR. LOCKE: We haven't seen Exhibit</p> <p>14 No.--</p> <p>15 Q (By Mr. Williams) Did you hear my question?</p> <p>16 A No-- yes.</p> <p>17 Q You're quoted in this article-- strike that.</p> <p>18 The title of your article is, "How to reduce the</p> <p>19 odds of getting cancer," right?</p> <p>20 A Yes.</p> <p>21 Q You are quoted in this article as saying there are steps</p> <p>22 people can take to absolutely cut their risk of getting</p> <p>23 cancer, true?</p> <p>24 A Yes.</p> <p>25 Q Directly under the title there's a quote that says,</p>



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<p>1 "There are steps you can take that will absolutely cut</p> <p>2 your risk, says Fred Hutch's doctor Anne McTiernan, who</p> <p>3 contributed to a new report on diet, nutrition, physical</p> <p>4 activity and cancer," did I read that right?</p> <p>5 A Yes.</p> <p>6 Q Now, at the time that you were writing this commentary, I</p> <p>7 take it that you were not limited in any way in what you</p> <p>8 could talk about as a way that someone could cut their</p> <p>9 risk of getting cancer?</p> <p>10 No one was editing your words, true?</p> <p>11 A That's not true.</p> <p>12 The communications department has final say on what</p> <p>13 goes out from our institution, so I don't have full</p> <p>14 leeway of what went out.</p> <p>15 They had asked me to write about something, with</p> <p>16 their help, their editing, on the new report by the World</p> <p>17 Cancer Research Fund, so it focused primarily on</p> <p>18 nutrition, physical activity, and diet information.</p> <p>19 Q Are you suggesting that you could not have referenced</p> <p>20 talcum powder or stopping the use of talcum powder as it</p> <p>21 relates to your view of ovarian cancers, ma'am?</p> <p>22 A I am saying I was asked to focus on these variables in</p> <p>23 this new report.</p> <p>24 Fred Hutchinson is-- the communications department</p> <p>25 is a news program-- sorry, a news service-- they call</p>	<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: When we do a causation</p> <p>3 analysis as epidemiologists, we primarily rely on results</p> <p>4 in humans and especially epidemiology, but we also look</p> <p>5 to see if there are plausible biologic mechanisms that</p> <p>6 can link what we see in the human data, in terms of</p> <p>7 exposure to risk of disease, so we do look at biological</p> <p>8 mechanisms as well.</p> <p>9 Q (By Mr. Williams) Much of epidemiologic observational</p> <p>10 research in cancer focuses on determining the</p> <p>11 associations between an exposure and an outcome, true or</p> <p>12 not true?</p> <p>13 A Yes, that's true.</p> <p>14 Q The mere existence of an association does not itself</p> <p>15 prove a cause and effect relationship between the</p> <p>16 exposure and the disease, right?</p> <p>17 A The existence of an association is typically part of the</p> <p>18 scientific data we would use in order to determine if</p> <p>19 it's a cause and effect, and there could be some-- some</p> <p>20 associations that would be so difficult to explain</p> <p>21 otherwise, that you would understand that that has to be</p> <p>22 a cause, but typically in the epidemiology of cancer, we</p> <p>23 are looking at both the results in human, human</p> <p>24 population studies, epidemiology studies, but we also</p> <p>25 look at plausible biologic mechanisms.</p>
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<p>1 themselves a news service, and they wanted me to talk</p> <p>2 about new results.</p> <p>3 I added-- I did add to try to avoid other</p> <p>4 carcinogens, and I specifically mentioned air pollution</p> <p>5 and asbestos as some things that affect many different</p> <p>6 cancers, but I was primarily tasked to talk about</p> <p>7 nutrition, physical activity, and diet, and especially</p> <p>8 since that was a new report.</p> <p>9 That's why this article is focused on that.</p> <p>10 Q Did you identify talc use as an actual or probable</p> <p>11 carcinogen of any kind of cancer in this article?</p> <p>12 A This was not focused on any particular risk factor, so I</p> <p>13 was talking about very generic environmental causes of</p> <p>14 cancer, and I can see that I did mention asbestos as an</p> <p>15 example, but I did not list all of the cancer-causing</p> <p>16 chemicals that can be encountered.</p> <p>17 Q In terms of your day-to-day research activities, those</p> <p>18 are in the field of epidemiology, correct?</p> <p>19 A Epidemiology and clinical trials.</p> <p>20 Some people consider that clinical research, and</p> <p>21 some consider it epidemiology, but I'm an epidemiologist</p> <p>22 and an internist.</p> <p>23 Q When it comes to assessing cause, epidemiology, your</p> <p>24 field, is only one part of the causation analysis; is</p> <p>25 that true?</p>	<p>1 Q Association is not synonymous with causation, is it,</p> <p>2 ma'am?</p> <p>3 A Association, correct, it's not exactly the same as</p> <p>4 causation.</p> <p>5 Q As you read the epidemiologic literature as part of your</p> <p>6 work in this matter, you considered the Bradford Hill</p> <p>7 aspects of causal inference, right?</p> <p>8 A That's correct.</p> <p>9 Q The continuous research project, for which you serve as a</p> <p>10 panel member, also uses the Bradford Hill criteria as the</p> <p>11 basis for its systematic review analyses, true?</p> <p>12 A The World Cancer Research Fund has a modified version of</p> <p>13 Bradford Hill.</p> <p>14 Most groups that are looking at these types of</p> <p>15 variables, and are looking at developing public</p> <p>16 recommendations, will use some kind of modification of</p> <p>17 Bradford-Hill-like criteria, so the World Cancer Research</p> <p>18 Fund has developed criteria that are very different in</p> <p>19 some way from other epidemiology studies, and</p> <p>20 particularly because they're focused on nutrition, and</p> <p>21 nutrition is a variable different from other types of</p> <p>22 exposures in terms of developing them.</p> <p>23 They also have further developed those criteria for</p> <p>24 survivorship, so it's not exactly a Bradford Hill</p> <p>25 analysis.</p>



<p style="text-align: right;">Page 110</p> <p>1 Q The Bradford Hill criteria are the basis for the</p> <p>2 Continuous Update Project systematic review analyses and</p> <p>3 the criteria for judging the evidence, true or not true?</p> <p>4 MS. PARFITT: Objection; form, asked</p> <p>5 and answered.</p> <p>6 THE WITNESS: I would say Bradford</p> <p>7 Hill criteria were considered in developing the</p> <p>8 guidelines for the systematic review interpretation.</p> <p>9 (Exhibit No. 10 marked</p> <p>10 for identification.)</p> <p>11</p> <p>12 Q (By Mr. Williams) Let me have you look at what we've</p> <p>13 marked as Exhibit No. 10.</p> <p>14 Exhibit No. 10 is a multi-page document from the</p> <p>15 World Cancer Research Fund entitled, "Judging the</p> <p>16 evidence," and dated 2018.</p> <p>17 Do you recognize this document?</p> <p>18 A Yes, I do.</p> <p>19 Q This document was published at a time when you were</p> <p>20 serving as a panelist for the World Cancer Research Fund?</p> <p>21 A It was developed before then, but it was published again</p> <p>22 at that time, yes.</p> <p>23 Q Let me have you look at Page 4.</p> <p>24 Page 4 sets forth how to cite the third expert</p> <p>25 report ; does it not?</p>	<p style="text-align: right;">Page 112</p> <p>1 That was my question.</p> <p>2 MS. PARFITT: Mr. Williams, if I could</p> <p>3 just say, she is a doctor, if we could refer to her as</p> <p>4 "Doctor."</p> <p>5 MR. WILLIAMS: I'm sorry. Pardon me.</p> <p>6 Q (By Mr. Williams) Dr. McTiernan, excuse me, is that last</p> <p>7 sentence of the second paragraph on Page 5 accurate or</p> <p>8 not?</p> <p>9 MS. PARFITT: Thank you.</p> <p>10 Objection.</p> <p>11 THE WITNESS: When I said "basis," I</p> <p>12 would say it's the beginning because it was revised quite</p> <p>13 a bit.</p> <p>14 I will add to that.</p> <p>15 There are things in this document, in this</p> <p>16 evidence-- "Judging the evidence" document that go much</p> <p>17 beyond what Bradford Hill aspects considered and are much</p> <p>18 more specific to these types of variables.</p> <p>19 Q (By Mr. Williams) Let me have you turn to-- let's take a</p> <p>20 look back at the exhibit that we marked as Exhibit No. 5.</p> <p>21 Exhibit No. 5 is the 2018 revised report.</p> <p>22 Do you have that in front of you?</p> <p>23 A Yes.</p> <p>24 Q This document at Page 9 sets forth the methodology for</p> <p>25 the report.</p>
<p style="text-align: right;">Page 111</p> <p>1 A How to cite the whole report, yes.</p> <p>2 Q It was contemplated at the time that this document,</p> <p>3 "Judging the evidence," was published, that it could be</p> <p>4 cited by experts, correct?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: Yes.</p> <p>7 Q (By Mr. Williams) Look at Page 5, if you would.</p> <p>8 A (Witness complies.)</p> <p>9 Q Page 5 under the title, "Introduction," the second full</p> <p>10 paragraph, I will direct you to the last sentence. It</p> <p>11 says, "The Bradford Hill criteria are the basis for the</p> <p>12 Continuous Update Project, CUP, systematic review</p> <p>13 analyses and the criteria for judging evidence."</p> <p>14 Do you see that?</p> <p>15 A Yes, I do.</p> <p>16 Q Is that an accurate statement?</p> <p>17 A I would say it's the beginning because they did change,</p> <p>18 and it spanned quite a bit compared to Bradford Hill.</p> <p>19 Bradford Hill's speech, when he developed it and</p> <p>20 when the result was published in the World Society of</p> <p>21 Medicine, was very basic, did not have the many criteria</p> <p>22 that World Cancer Research Fund uses, and their criteria,</p> <p>23 the way they developed it, beyond Bradford Hill, was</p> <p>24 because of the nutrition-related variables.</p> <p>25 Q Is it an accurate statement or not, ma'am?</p>	<p style="text-align: right;">Page 113</p> <p>1 Do you see that on Page 9?</p> <p>2 A Yes.</p> <p>3 Q And it says, "Through this process," and this is the</p> <p>4 third paragraph on that page. "Through this process the</p> <p>5 CUP ensures that everyone, including policy-makers,</p> <p>6 health professionals, and members of the public, has</p> <p>7 access to the most up-to-date information on how to</p> <p>8 reduce the risk of developing cancer."</p> <p>9 Do you see that?</p> <p>10 A No-- so you are on Page 9?</p> <p>11 Which paragraph?</p> <p>12 Q I'm sorry, Page 4. I misspoke.</p> <p>13 MS. PARFITT: Thank you.</p> <p>14 Q (By Mr. Williams) Pardon me, ma'am-- Doctor.</p> <p>15 Page 4, third paragraph, under "Our Continuous</p> <p>16 Update Project."</p> <p>17 Do you see that?</p> <p>18 A Yes.</p> <p>19 Q The whole purpose of the continuous update process is to</p> <p>20 try to ensure that members of the public have access to</p> <p>21 the most up-to-date information on how to reduce the risk</p> <p>22 of developing cancer, correct?</p> <p>23 MS. PARFITT: Objection; misstates the</p> <p>24 document.</p> <p>25 THE WITNESS: If you are looking at</p>

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<p>1 that sentence, you would also have to put it in context</p> <p>2 of what this report is.</p> <p>3 It's related to diet, nutrition, physical activity</p> <p>4 and cancer.</p> <p>5 It is not all potential causes of cancer that an</p> <p>6 individual could modify in order to reduce risk.</p> <p>7 We are talking only about diet, nutrition, and</p> <p>8 physical activity.</p> <p>9 Q (By Mr. Williams) Let's look at Page No. 9 of this</p> <p>10 exhibit.</p> <p>11 At the end of the first paragraph, under the</p> <p>12 heading, "Methodology," it says, halfway down that</p> <p>13 paragraph, "The literature search was restricted to</p> <p>14 Medline and included only randomized controlled trials,</p> <p>15 cohort and case-control studies. Due to their</p> <p>16 methodological limitations, case-control studies were not</p> <p>17 analyzed in the Ovarian Cancer SLR 2013."</p> <p>18 Do you see that?</p> <p>19 A Yes.</p> <p>20 Q And "SLR" refers to "systematic literature review"?</p> <p>21 A Yes, it does.</p> <p>22 Q When you were considering the literature in your work for</p> <p>23 the World Cancer Research Fund to determine what causes</p> <p>24 cancer, it is accurate that your panel did not look at</p> <p>25 any case-control studies?</p>	<p>1 and those can have case-control studies in them.</p> <p>2 It's just that when they do their meta-analyses,</p> <p>3 which is actually looking at data from the various</p> <p>4 studies, they make the choice for nutrition variables to</p> <p>5 focus on cohort studies for some cancers and some</p> <p>6 exposures.</p> <p>7 As I mentioned, arsenic, there was some other</p> <p>8 exposures, like very hot teas that were studied in</p> <p>9 case-control studies, so that's not a complete sentence--</p> <p>10 statement for all of the projects.</p> <p>11 MR. WILLIAMS: I move to strike that</p> <p>12 as nonresponsive.</p> <p>13 Q (By Mr. Williams) My question to you is this:</p> <p>14 The last sentence under "Methodology" on Page 9 of</p> <p>15 this exhibit, Exhibit No. 5, says that "Due to their</p> <p>16 methodological limitations, case-control studies were not</p> <p>17 analyzed in the Ovarian Cancer SLR 2013."</p> <p>18 That's what it says, right?</p> <p>19 A And I was explaining what it means.</p> <p>20 Q You would agree with me that each study design, cohort</p> <p>21 study, case-control study, other types of studies, has</p> <p>22 its advantages and limitations, correct?</p> <p>23 A That's true.</p> <p>24 Q And you would agree that the hierarchy of epidemiological</p> <p>25 evidence places cohort studies above case-control</p>
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<p>1 A That's not true for the entire work that we did.</p> <p>2 For some of the cancers and some of the exposures we</p> <p>3 did include case-control studies; for example, arsenic</p> <p>4 and some other carcinogens.</p> <p>5 When I mentioned that the Bradford Hill aspects were</p> <p>6 extended for this analysis, it is particularly because of</p> <p>7 nutrition variables.</p> <p>8 Nutrition variables are very difficult to ascertain</p> <p>9 for exposure because as opposed to the use of talcum</p> <p>10 powder products, which might be used once or twice a day,</p> <p>11 nutrition variables are occurring sometimes 50 to 100</p> <p>12 times a day.</p> <p>13 The amount that people eat, what they're eating, how</p> <p>14 often they're eating, the variables are so difficult to</p> <p>15 collect, that the results from case-control studies are a</p> <p>16 concern to some investigators.</p> <p>17 Many epidemiologists disagree with this choice of</p> <p>18 what World Cancer Research Fund decided to do.</p> <p>19 When it says-- however, I should also mention when</p> <p>20 it says, "analyzed," that's analyzed for the</p> <p>21 meta-analysis.</p> <p>22 The World Cancer Research Fund, when they do the</p> <p>23 systematic reviews, also looks for pooled analyses and</p> <p>24 meta-analyses, and they present them in the SLR, and</p> <p>25 reports will have information from those other reports,</p>	<p>1 studies?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: I would say the</p> <p>4 hierarchy of epidemiology evidence depends entirely on</p> <p>5 the question under review.</p> <p>6 If you have an exposure, which is very difficult to</p> <p>7 measure and which can change over time or which you are</p> <p>8 trying to determine lifetime exposure, then often it's</p> <p>9 more-- it's easier to do that in a case-control study.</p> <p>10 The case-control studies that were reviewed for the</p> <p>11 talcum powder product used and ovarian cancer risk</p> <p>12 primarily used interview questionnaires, so an</p> <p>13 interviewer spending time, sometimes several hours with a</p> <p>14 patient in control, to determine lifetime exposures.</p> <p>15 The cohort studies, however, typically, and</p> <p>16 especially the three cohort studies that were included in</p> <p>17 this review and that have been published on ovarian</p> <p>18 cancer and talcum powder products, those studies were</p> <p>19 designed to look at multiple diseases.</p> <p>20 Nurses' Health Study was started to--</p> <p>21 Q (By Mr. Williams) Ma'am, I am going to have to cut you</p> <p>22 off because-- look, when I ask you questions, I need you</p> <p>23 to answer the question that I've asked. Otherwise, you</p> <p>24 could just talk for a half an hour, so if you would,</p> <p>25 please, Doctor, just focus on the question that I'm</p>

<p style="text-align: right;">Page 118</p> <p>1 asking you.</p> <p>2 The question that I'm asking you is:</p> <p>3 As a matter of epidemiological practice in your line</p> <p>4 of work, is it true or not true that case-- excuse me,</p> <p>5 that cohort studies are placed higher in the hierarchy</p> <p>6 than case-control studies?</p> <p>7 If the answer is that's not true, please just say</p> <p>8 it's not true.</p> <p>9 MS. PARFITT: Objection to form; asked</p> <p>10 and answered.</p> <p>11 THE WITNESS: I think-- yeah, I did</p> <p>12 try to answer that before. I will try to do it better</p> <p>13 this time.</p> <p>14 For one thing, I am not sure what hierarchy you are</p> <p>15 referring to, but what I'm saying is that depending on</p> <p>16 the question, one type of study could be preferable to</p> <p>17 another, but in general all of the studies provide</p> <p>18 information, and we look at the totality of evidence.</p> <p>19 Q (By Mr. Williams) So it is your view that there is no</p> <p>20 generally accepted hierarchy of epidemiological evidence?</p> <p>21 MS. PARFITT: Objection; form,</p> <p>22 misstates her testimony.</p> <p>23 THE WITNESS: I think it depends</p> <p>24 entirely on what the question is.</p> <p>25 Q (By Mr. Williams) Let's look at Exhibit No. 10, which is</p>	<p style="text-align: right;">Page 120</p> <p>1 question to you now is:</p> <p>2 Is it your testimony that there is in fact no</p> <p>3 generally accepted hierarchy of epidemiological evidence</p> <p>4 that places cohort studies above case-control studies?</p> <p>5 MS. PARFITT: Objection.</p> <p>6 THE WITNESS: And I would again say it</p> <p>7 depends entirely on the question, the scientific</p> <p>8 question.</p> <p>9 Q (By Mr. Williams) Here this references that cohort</p> <p>10 studies are likely to be the main source of evidence</p> <p>11 owing to the long latent period for cancer and owing to</p> <p>12 their prospective design.</p> <p>13 Those are the two concepts that it mentions in that</p> <p>14 sentence, correct?</p> <p>15 A That's what that mentions, yes.</p> <p>16 Q And the latent period for cancer refers to the fact that</p> <p>17 exposure to a substance can sometimes take some time</p> <p>18 before cancer is developed, right?</p> <p>19 A That's correct.</p> <p>20 Q That's the latency period?</p> <p>21 A Yes.</p> <p>22 Q And the idea of a prospective cohort study is that people</p> <p>23 are asked about their-- what they do and put on and in</p> <p>24 their bodies right now when they are healthy, and then</p> <p>25 they are followed along, correct?</p>
<p style="text-align: right;">Page 119</p> <p>1 the "Judging the evidence" document from 2018 from the</p> <p>2 World Cancer Research Fund, and I will direct your</p> <p>3 attention to the seventh page.</p> <p>4 At the bottom of Page 7 of this exhibit, Exhibit</p> <p>5 No. 10, it has a section that says, "Study design," that</p> <p>6 says, "Each study design has its advantages and</p> <p>7 limitations. The hierarchy of epidemiological evidence</p> <p>8 places cohort studies above case-control studies, with</p> <p>9 ecological studies and case reports at the bottom.</p> <p>10 "There are merits in considering a number of</p> <p>11 different study designs. Cohort studies are likely to be</p> <p>12 the main source of evidence owing to the long latent</p> <p>13 period for cancer to develop and also to their</p> <p>14 prospective design"--</p> <p>15 A I'm sorry, can you say where you're reading from?</p> <p>16 MS. PARFITT: 7. He's right here.</p> <p>17 THE WITNESS: Okay.</p> <p>18 Q (By Mr. Williams) And I've read through that heading,</p> <p>19 "Study design," through to the last sentence that says,</p> <p>20 "However, in some circumstances case-control studies and</p> <p>21 ecological studies may also make a useful contribution to</p> <p>22 the evidence," and it refers to Section 7.</p> <p>23 Do you see that?</p> <p>24 A Yes.</p> <p>25 Q Now, we are going to go to Section 7 in a minute, but my</p>	<p style="text-align: right;">Page 121</p> <p>1 A That's correct.</p> <p>2 Q Okay. And retrospective case-control studies are</p> <p>3 backwards-looking where people are asked questions after</p> <p>4 they have contracted a disease and they are asked to</p> <p>5 recall what they put on and in their bodies, true?</p> <p>6 A So that is typical.</p> <p>7 Cohort studies, by the way, could also ask</p> <p>8 retrospectively what somebody had done over their</p> <p>9 lifetime.</p> <p>10 In this particular case, with talcum powder</p> <p>11 products, they did, but I have seen many studies do that.</p> <p>12 They can do a lifetime exposure, and then if-- the</p> <p>13 better cohort studies focused on certain-- depending on</p> <p>14 the question, they update their data so that then you</p> <p>15 could have a lifetime exposure variable from a cohort</p> <p>16 study.</p> <p>17 For the-- in terms of long latent period for cancer,</p> <p>18 case-control studies, if they're asking about lifetime</p> <p>19 exposure and collecting that information, that would not</p> <p>20 be an issue or a problem for case-control studies.</p> <p>21 Q Let me have you turn to Section No. 7, which is on Page</p> <p>22 21.</p> <p>23 That's the section that's referred to at the end of</p> <p>24 the page we were just looking at, the study design</p> <p>25 section referring to Section 7, so I want to go there.</p>

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<p>1 Do you have Page 21 in front of you?</p> <p>2 A Yeah.</p> <p>3 Q In the left-hand column under Section 7, "Evidence</p> <p>4 collated for the Continuous Update Project," at the very</p> <p>5 bottom, it has the sentence that says, "The first stage</p> <p>6 of the SLRs was a comprehensive search using a</p> <p>7 standardized search strategy for the scientific</p> <p>8 literature for randomized trials and cohort studies</p> <p>9 published since 2006 using Medline. Because case-control</p> <p>10 studies are particularly prone to recall (and other)</p> <p>11 bias, they were not routinely reviewed"--</p> <p>12 A Where are you again? Okay. Sorry.</p> <p>13 MS. PARFITT: Just give her a moment,</p> <p>14 Mr. Williams, to catch up.</p> <p>15 Q (By Mr. Williams) Do you see where I am?</p> <p>16 A Yes.</p> <p>17 Q In the right-hand column of Page 21 it says, "Because</p> <p>18 case-control studies are particularly prone to recall</p> <p>19 (and other) bias, they were not routinely reviewed.</p> <p>20 "However, if there were no or very few RCTs or</p> <p>21 cohort studies, they were included."</p> <p>22 Do you see that?</p> <p>23 A Yes.</p> <p>24 Q In the case of talc and ovarian cancer, as of 2018, is it</p> <p>25 accurate to say that there are five cohort studies that</p>	<p>1 showed that there was no statistically significant</p> <p>2 relationship between talc use and ovarian cancer,</p> <p>3 correct?</p> <p>4 MS. PARFITT: Objection; form.</p> <p>5 THE WITNESS: One of those studies did</p> <p>6 show a statistically significant association with use of</p> <p>7 talcum powder products and risk of serous ovarian cancer,</p> <p>8 and that was the Gertig study, but I also did an analysis</p> <p>9 showing there was insufficient number of cases in all</p> <p>10 three of those studies in order to find a statistically</p> <p>11 significant result.</p> <p>12 The driver of statistical significance is the number</p> <p>13 of cases in a study, regardless of whether it's a cohort</p> <p>14 study or case-control study.</p> <p>15 Q (By Mr. Williams) We will get to the number of cases in</p> <p>16 a moment, but with respect to the Gertig study, you are</p> <p>17 aware and came across in your review, because you</p> <p>18 referenced them in your report, that that Gertig study</p> <p>19 was updated in 2008 and 2010 under the name "Gates,"</p> <p>20 correct?</p> <p>21 MS. PARFITT: Objection; form.</p> <p>22 THE WITNESS: 2008 I would not call an</p> <p>23 update.</p> <p>24 It only included 200 cases from the Nurses' Health</p> <p>25 Study. It also included other cases from the New England</p>
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<p>1 you have had the benefit of reviewing?</p> <p>2 A That is not correct.</p> <p>3 In the three cohort studies, one of which had three</p> <p>4 publications with different numbers of cases in them--</p> <p>5 there are three cohort studies.</p> <p>6 Q So if we count the study that has three different cohort</p> <p>7 studies within it, and then add the other two cohort</p> <p>8 studies, we would get to five; would we not?</p> <p>9 MS. PARFITT: Objection; form.</p> <p>10 THE WITNESS: I repeat, the three</p> <p>11 cohort studies, just that one of them has three</p> <p>12 publications.</p> <p>13 Q (By Mr. Williams) And do you consider three cohort</p> <p>14 studies, one of which had three separate sets of data, to</p> <p>15 be insufficient to do an analysis of whether talc causes</p> <p>16 ovarian cancer?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 THE WITNESS: I would consider those</p> <p>19 three-- what I would do is look at the individual studies</p> <p>20 of those three studies. I would look at how the data</p> <p>21 were collected and whether you can get the information</p> <p>22 that you want to look at your question, before deciding</p> <p>23 that they were sufficient on their own.</p> <p>24 Q (By Mr. Williams) Every single cohort study that you</p> <p>25 looked at in this case, for your work in this litigation,</p>	<p>1 case-control study, so when you look at just the Nurses'</p> <p>2 Health Study, part of it was only 200 cases, and it is</p> <p>3 very difficult to determine which cases those were.</p> <p>4 The second update wasn't an update, but at that time</p> <p>5 they ended up looking at a different variable, a</p> <p>6 different comparison.</p> <p>7 The first study compared no use, never-users, to</p> <p>8 users of different categories.</p> <p>9 The second-- the third study compared-- combined</p> <p>10 never-users with use of less than once a week, so you</p> <p>11 have a very different comparison, so I think that was--</p> <p>12 that was concerning.</p> <p>13 It's not clear it's a real update-- the data aren't</p> <p>14 really there.</p> <p>15 That third study also didn't focus just on talc.</p> <p>16 Talc was just one of the variables in the study.</p> <p>17 Q (By Mr. Williams) To the extent that the 2010 study by</p> <p>18 Gates, that update-- first of all, the 2010 update wasn't</p> <p>19 an update.</p> <p>20 You just said that yourself, correct, Doctor?</p> <p>21 MS. PARFITT: Objection.</p> <p>22 THE WITNESS: It was an update of</p> <p>23 cases.</p> <p>24 It is not clear it was an update of the data.</p> <p>25 Q (By Mr. Williams) True or not true, the 2010 Gates</p>

<p style="text-align: right;">Page 126</p> <p>1 update did not show a statistically significant increased</p> <p>2 risk of serous invasive ovarian cancer?</p> <p>3 MS. PARFITT: Objection.</p> <p>4 THE WITNESS: It did not show a</p> <p>5 statistically significant association, correct.</p> <p>6 Q (By Mr. Williams) Can you identify any cohort study that</p> <p>7 concluded that there was a statistically significant</p> <p>8 overall association between talc and ovarian cancer?</p> <p>9 MS. PARFITT: Objection; form.</p> <p>10 THE WITNESS: So you are talking about</p> <p>11 for talc and any type of epithelial ovarian cancer?</p> <p>12 Q (By Mr. Williams) Any statistically significant overall</p> <p>13 association between talc and ovarian cancer.</p> <p>14 A That's correct, I didn't have sufficient sample size to</p> <p>15 do it.</p> <p>16 Q The answer to my question is that you cannot identify any</p> <p>17 cohort study concluding that there was a statistically</p> <p>18 significant overall association between talc and ovarian</p> <p>19 cancer, correct?</p> <p>20 MS. PARFITT: Objection to form; asked</p> <p>21 and answered.</p> <p>22 Q (By Mr. Williams) You may answer, Doctor.</p> <p>23 A So my answer is the same, that statistical significance</p> <p>24 is not seen because the sample size is too small.</p> <p>25 Q Is there any other reason why statistical significance</p>	<p style="text-align: right;">Page 128</p> <p>1 12:30? What's your pleasure?</p> <p>2 MS. PARFITT: Can we go off the</p> <p>3 record?</p> <p>4 MR. WILLIAMS: Let's go off the</p> <p>5 record.</p> <p>6 VIDEOGRAPHER: Going off record, the</p> <p>7 time is 12:07 p.m.</p> <p>8 (Recess 12:07 to 12:0 p.m.)</p> <p>9</p> <p>10 VIDEOGRAPHER: We are back on the</p> <p>11 record. The time is 12:09 p.m.</p> <p>12 Q (By Mr. Williams) Dr. McTiernan, would you agree that if</p> <p>13 you had only looked at the cohort studies in this case,</p> <p>14 like it is suggested is appropriate in the World Cancer</p> <p>15 Research Fund "Judging the evidence" document, Exhibit</p> <p>16 No. 10, that you would not have been able to opine that</p> <p>17 talcum powder causes ovarian cancer?</p> <p>18 MS. PARFITT: Objection; form.</p> <p>19 THE WITNESS: First I want to respond</p> <p>20 by characterizing the World Cancer Research Fund</p> <p>21 document, that they're referring to nutrition variables,</p> <p>22 so that is why they consider case-control studies to be a</p> <p>23 much lower hierarchy than cohort studies.</p> <p>24 In terms of what was seen in the cohort studies, we</p> <p>25 did see, with the Nurses' Health Study, elevated risk of</p>
<p style="text-align: right;">Page 127</p> <p>1 was not seen besides the sample size being too small?</p> <p>2 A Sample size is one of the major drivers.</p> <p>3 The other thing is there is a lot of variability</p> <p>4 around the point estimate, the relative risk.</p> <p>5 When you see a sample size that's that small, that's</p> <p>6 the major thing you start thinking about.</p> <p>7 Q Other than sample size and variability, is there any</p> <p>8 other factor that you believe makes the cohort studies</p> <p>9 unreliable?</p> <p>10 A I don't think I used the word "unreliable." I used the</p> <p>11 word "not statistically significant."</p> <p>12 MS. PARFITT: Objection.</p> <p>13 Q (By Mr. Williams) Other than sample size and</p> <p>14 variability, is there anything else that bears upon</p> <p>15 statistical significance that is important?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 You are referring to the collective group of cohort</p> <p>18 studies?</p> <p>19 THE WITNESS: The statistical</p> <p>20 significance-- you are not talking about the effects.</p> <p>21 You are talking about statistical significance. Those</p> <p>22 are the things that would drive it, in my opinion.</p> <p>23 MR. WILLIAMS: Counsel, I am going to</p> <p>24 go to a different topic.</p> <p>25 Do you want to take lunch now? Do you want to go</p>	<p style="text-align: right;">Page 129</p> <p>1 serous cancer.</p> <p>2 We also saw in the two cohort studies elevated risk</p> <p>3 that was not statistically significant, and I-- my</p> <p>4 opinion is that's because the sample size was small.</p> <p>5 In answer, two of the three cohort studies did show</p> <p>6 elevated risk of ovarian cancer, but they were not</p> <p>7 statistically significant, with the exception to the</p> <p>8 serous subtype in the Nurses' Health Study.</p> <p>9 Q (By Mr. Williams) Have you completed your answer?</p> <p>10 A Yes.</p> <p>11 Q The only type of cancer for which there was a</p> <p>12 statistically significant finding in one of the studies</p> <p>13 related to serous invasive ovarian cancer, correct?</p> <p>14 A Only one type showing statistical significance around</p> <p>15 that relative risk, yes.</p> <p>16 Q And that was the Gertig 2000 study?</p> <p>17 A Yes.</p> <p>18 The--</p> <p>19 Q Ma'am, you have answered my question.</p> <p>20 Was the Gertig 2000 study the only study where there</p> <p>21 was a statistically significant finding that serous</p> <p>22 invasive ovarian cancer was associated with talc use?</p> <p>23 MS. PARFITT: Objection; form.</p> <p>24 THE WITNESS: For the cohort studies,</p> <p>25 yes, that's correct.</p>



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<p>1 Q (By Mr. Williams) I take it you and I disagree as to</p> <p>2 whether or not the Gates 2010 update showed that that</p> <p>3 previously seen statistically significant increased risk</p> <p>4 for serous invasive cancer went away?</p> <p>5 You think it did not go away. I represented to you</p> <p>6 that the study says that it did go away, right?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 THE WITNESS: My issue with them is</p> <p>9 not-- is that different comparisons were made.</p> <p>10 The first one looked at never-use versus ever-use--</p> <p>11 Q (By Mr. Williams) You have already explained that,</p> <p>12 ma'am--</p> <p>13 MS. PARFITT: Please allow her to</p> <p>14 complete.</p> <p>15 THE WITNESS: I am just referring to</p> <p>16 my answer.</p> <p>17 The second study, the 2010 Gates study, was then</p> <p>18 comparing never-user plus less than once a week use</p> <p>19 versus greater use, so it's a different comparison.</p> <p>20 That's going to dampen, going to lower the relative risk</p> <p>21 by putting some of the users in with the nonusers.</p> <p>22 Q (By Mr. Williams) The Gates 2010 study did not show a</p> <p>23 statistically significant increased risk for serous</p> <p>24 invasive ovarian cancer, true or not true?</p> <p>25 MS. PARFITT: Objection; form, asked</p>	<p>1 World Cancer Research report or my report?</p> <p>2 Q (By Mr. Williams) I am referring to--</p> <p>3 A For the talcum powder products--</p> <p>4 Q I'll restate the question.</p> <p>5 For purposes of preparing your report, Exhibit No. 2</p> <p>6 for this deposition, which is the report you prepared for</p> <p>7 this litigation-- do you have that in mind?</p> <p>8 A Yes.</p> <p>9 Q It is true that you relied heavily on Exhibit No. 10, the</p> <p>10 "Judging the evidence" document, in preparing your</p> <p>11 report, which is Exhibit No. 2?</p> <p>12 MS. PARFITT: Objection; form.</p> <p>13 THE WITNESS: I didn't rely heavily.</p> <p>14 I cited it as some of the methods of reviewing</p> <p>15 meta-analyses. I used some of the methods that I used</p> <p>16 for that as well as what was used for the government</p> <p>17 physical activity guidelines, but I did not use this</p> <p>18 entirely.</p> <p>19 In terms of determining causality, I used-- I went</p> <p>20 back to the original Bradford Hill aspects, listed</p> <p>21 aspects, to determine causality. I did not use the</p> <p>22 guidelines for the CUP analysis in determining whether</p> <p>23 the association that's seen between talcum powder</p> <p>24 products and risk of ovarian cancer meets criteria for</p> <p>25 causal.</p>
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<p>1 and answered.</p> <p>2 THE WITNESS: It showed a six percent</p> <p>3 increase in risk that was not statistically significant,</p> <p>4 and it's not comparing nonusers to users. It's comparing</p> <p>5 nonusers plus less-than-once-a-week users to more-often</p> <p>6 users.</p> <p>7 Q (By Mr. Williams) Let me ask you to look, Doctor, at</p> <p>8 Exhibit No. 10--</p> <p>9 A Which one?</p> <p>10 Q Exhibit No. 10, the "Judging the risk" document from</p> <p>11 2018-- excuse me, "Judging the evidence."</p> <p>12 I misspoke.</p> <p>13 First, I haven't done this yet, but if you look at</p> <p>14 Page 30, the acknowledgments section, it lists you as a</p> <p>15 panel member for this review, correct?</p> <p>16 A Yes.</p> <p>17 Q It is true that you relied very heavily on this document,</p> <p>18 that is Exhibit No. 10, in drafting your report for this</p> <p>19 case?</p> <p>20 MS. PARFITT: Objection; misstates</p> <p>21 testimony.</p> <p>22 THE WITNESS: I did not draft this</p> <p>23 report.</p> <p>24 Is that what you mean?</p> <p>25 The World Cancer-- so you are talking about the</p>	<p>1 Q (By Mr. Williams) Let me be very specific about what I</p> <p>2 mean.</p> <p>3 When you were typing up Exhibit No. 2, your report</p> <p>4 for this case, you literally had this exhibit, Exhibit</p> <p>5 No. 10, next to you as you typed?</p> <p>6 MS. PARFITT: Objection.</p> <p>7 Q (By Mr. Williams) True or not true?</p> <p>8 MS. PARFITT: Objection; form.</p> <p>9 THE WITNESS: It's not true.</p> <p>10 Q (By Mr. Williams) Is it your testimony that you prepared</p> <p>11 your report without any reference at all to any part of</p> <p>12 Exhibit No. 10?</p> <p>13 A I did reference it. It's one of the references here.</p> <p>14 Q Show me that, if you would.</p> <p>15 A I think-- I used-- I included the website.</p> <p>16 Q You included the website for the 2014 report on Page 5 of</p> <p>17 your report, but if you did refer to this document,</p> <p>18 Exhibit No. 10, in your references or anywhere else,</p> <p>19 please let me know where that is.</p> <p>20 A So I don't see it if I did.</p> <p>21 Q Have you completed your answer?</p> <p>22 A What was the question again?</p> <p>23 Q I was asking you to point out for me--</p> <p>24 A Did I refer to it or did I reference it?</p> <p>25 I may not have referenced it.</p>



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<p>1 I thought I had.</p> <p>2 Yeah, I just have the website here.</p> <p>3 Q Let me refer you to your report in this case, Exhibit</p> <p>4 No. 2, and ask you to turn to Page 10.</p> <p>5 You have a heading that says, "The science of</p> <p>6 epidemiology" at Page 10.</p> <p>7 Do you see that?</p> <p>8 A Yes.</p> <p>9 Q And with the first paragraph there, starting about a</p> <p>10 third of the way into the paragraph, you write,</p> <p>11 "Epidemiological research describes and seeks to explain</p> <p>12 the distribution of health and disease within human</p> <p>13 populations."</p> <p>14 Did I read that correctly?</p> <p>15 A Yes.</p> <p>16 Q And skipping a sentence, you write, "This type of</p> <p>17 investigation is known as observational. By relating</p> <p>18 differences in circumstances and behavior to differences</p> <p>19 in the incidence of disease, associations are identified</p> <p>20 that may or may not be causal."</p> <p>21 Is that what it says?</p> <p>22 A Yes.</p> <p>23 Q And then the first sentence of the next paragraph says,</p> <p>24 "In epidemiological studies, an exposure is a factor or</p> <p>25 condition that may or may not influence the risk of</p>	<p>1 Is it accurate to say that the sentences that are</p> <p>2 set forth under that heading, "Epidemiological evidence,"</p> <p>3 are identical to sentences found in your report on Page</p> <p>4 10, with one exception, that there is a sentence that</p> <p>5 appears in your report that does not appear on Page 6 of</p> <p>6 Exhibit No. 10?</p> <p>7 MS. PARFITT: Object to the form of</p> <p>8 the question.</p> <p>9 THE WITNESS: I think you are talking</p> <p>10 about the sentences up here.</p> <p>11 Q (By Mr. Williams) I am actually talking about the three</p> <p>12 sentences that I read from Page 10 of your report, two</p> <p>13 sentences from the first paragraph, and one sentence, the</p> <p>14 first sentence from the second paragraph.</p> <p>15 Those three sentences are identical, word for word,</p> <p>16 to the sentences that appear on Page 6 of Exhibit No. 10?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 Q (By Mr. Williams) Correct?</p> <p>19 A Yes.</p> <p>20 Q Now, just so we're clear, did you provide the people who</p> <p>21 wrote the text of the World Cancer Research Fund a copy</p> <p>22 of your expert report in this case when this document,</p> <p>23 "Judging the evidence" was prepared?</p> <p>24 A No, they did not get a copy of this.</p> <p>25 Nobody has seen it, other than Ms. Parfitt and her</p>
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<p>1 disease," right?</p> <p>2 A Yes.</p> <p>3 Q Throughout your report you included a lot of citations to</p> <p>4 works that you relied upon, correct?</p> <p>5 A Yes.</p> <p>6 Q Your reference section includes, I think we said, 127</p> <p>7 citations, right?</p> <p>8 A Yes.</p> <p>9 Q You did not provide a citation for any of the sentences</p> <p>10 that we just read, right?</p> <p>11 A That is not here, no.</p> <p>12 Q And by that I mean there is no reference to a footnote,</p> <p>13 there is no reference to any of the 127 items in the back</p> <p>14 of your report, correct?</p> <p>15 A That's correct.</p> <p>16 Q Now, turn back to the "Judging the evidence" document,</p> <p>17 which we marked as Exhibit No. 10, and I will ask you to</p> <p>18 turn to Page 6 under the heading, "Epidemiological</p> <p>19 evidence."</p> <p>20 Right underneath that heading the "Judging the</p> <p>21 evidence" document from the World Cancer Research Fund</p> <p>22 says, and I'm quoting, "Epidemiological research</p> <p>23 describes and seeks to explain the distribution of health</p> <p>24 and disease within human populations," and I will stop</p> <p>25 there.</p>	<p>1 colleagues.</p> <p>2 Q So to this day there is nobody from the WCRF who has seen</p> <p>3 your expert report in this litigation, correct?</p> <p>4 A That's correct.</p> <p>5 Q So the way this work was, you had in front of you Exhibit</p> <p>6 No. 10, and you prepared-- took out sentences from the</p> <p>7 WCRF document and included them word for word in your</p> <p>8 report, correct?</p> <p>9 MS. PARFITT: Objection; form.</p> <p>10 THE WITNESS: I can't recall where I</p> <p>11 took this.</p> <p>12 I have many different documents where I have</p> <p>13 information about what epidemiology is.</p> <p>14 If I took it from here, I should have cited it, but</p> <p>15 I can't recall where exact sentences came from.</p> <p>16 Q (By Mr. Williams) Wherever you took it from--</p> <p>17 A I should have cited it.</p> <p>18 Q Whether it was the "Judging the evidence" document or</p> <p>19 someplace else, you didn't cite it?</p> <p>20 A I should have cited it, you're right.</p> <p>21 Q Now, we went through your expert report and the</p> <p>22 Continuous Update Project's "Judging the evidence"</p> <p>23 document, Exhibit No. 10, and we put the text side by</p> <p>24 side for various sections for ease of reference, and I'm</p> <p>25 going to pass those out to you, and we'll mark it as</p>

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<p>1 Exhibit No. 11.</p> <p>2 We will give it to Counsel.</p> <p>3 (Exhibit No. 11 marked</p> <p>4 for identification.)</p> <p>5</p> <p>6 Q (By Mr. Williams) Now, what we set forth here are a</p> <p>7 total of 13 different places where the language from the</p> <p>8 "Judging the evidence" report was used word for word,</p> <p>9 with some exceptions, in your report.</p> <p>10 Do you see that?</p> <p>11 I am not asking you to agree or disagree, but let me</p> <p>12 ask you to see that there are 13 different examples where</p> <p>13 the language is either word for word or roughly word for</p> <p>14 word used in your report, taking language that also</p> <p>15 appears in the "Judging the evidence" report.</p> <p>16 Do you see that?</p> <p>17 Take your time to look through there.</p> <p>18 MS. PARFITT: Objection to form.</p> <p>19 THE WITNESS: I can see that some of</p> <p>20 these are very common epidemiologic terms.</p> <p>21 Q (By Mr. Williams) Let's look for a little-- why don't</p> <p>22 you put that to one side for a moment and let me just ask</p> <p>23 you some other questions, and then we'll take lunch.</p> <p>24 I want to discuss a few places where it appears that</p> <p>25 you copied from the "Judging the evidence" document and</p>	<p>1 "The combination of data from multiple studies</p> <p>2 creates a larger data set and increased statistical</p> <p>3 power."</p> <p>4 Did I read that right from Exhibit No. 10?</p> <p>5 A Yes.</p> <p>6 Q Now, when you prepared your litigation report, you copied</p> <p>7 a lot of the language verbatim into your litigation</p> <p>8 report but made a few changes.</p> <p>9 Have you noticed those?</p> <p>10 MS. PARFITT: Objection to that form.</p> <p>11 Q (By Mr. Williams) Let me refer you to Exhibit No. 2,</p> <p>12 Page 22 of your report.</p> <p>13 Exhibit No. 2, Page 22.</p> <p>14 I would ask you to keep Exhibit No. 2, Page 22 open</p> <p>15 and keep Page 11 of Exhibit No. 10 open, and put them</p> <p>16 side by side.</p> <p>17 Referring you now to Page 22 of Exhibit No. 2, the</p> <p>18 first full paragraph on that page says, "Pooled analysis</p> <p>19 is a type of meta-analysis where original</p> <p>20 individual-level data from various published and/or</p> <p>21 unpublished epidemiological studies are combined and</p> <p>22 re-analyzed."</p> <p>23 Did I read that correctly from your report?</p> <p>24 A Yes.</p> <p>25 Q Now, when you wrote your report, the only difference</p>
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<p>1 made some changes.</p> <p>2 MS. PARFITT: And I will object to the</p> <p>3 form of that.</p> <p>4 Please continue.</p> <p>5 Q (By Mr. Williams) In describing what a pooled analysis</p> <p>6 is in the Continuous Update Project report, and I will</p> <p>7 refer you to Exhibit No. 10 at Page 11, in the right-hand</p> <p>8 column--</p> <p>9 MS. PARFITT: Just give us a moment--</p> <p>10 THE WITNESS: Exhibit No. 10?</p> <p>11 Q (By Mr. Williams) Right, Exhibit No. 10 at Page 11 on</p> <p>12 the right-hand column.</p> <p>13 There is a heading that says-- there's a paragraph</p> <p>14 that begins, "Pooled analysis," last paragraph on the</p> <p>15 page.</p> <p>16 Do you see that?</p> <p>17 A Mm-hm.</p> <p>18 Q Is that a "yes"?</p> <p>19 A Yes.</p> <p>20 Q In Exhibit No. 10, which is the "Judging the evidence"</p> <p>21 document, it says, "Pooled analysis is a type of</p> <p>22 meta-analysis in which original individual-level data</p> <p>23 from various published epidemiological studies of a</p> <p>24 similar type - usually prospective cohort studies - are</p> <p>25 combined and re-analyzed.</p>	<p>1 between the language that's set forth in Exhibit No. 10,</p> <p>2 in that first sentence, the only language that is added</p> <p>3 is "and/or unpublished."</p> <p>4 Do you see that?</p> <p>5 A Yes.</p> <p>6 Q So while the Exhibit No. 10, the "Judging the evidence"</p> <p>7 document that was put out by the World Cancer Research</p> <p>8 Fund, when they described a pooled analysis, they didn't</p> <p>9 say anything about unpublished studies, true?</p> <p>10 A So again--</p> <p>11 Q Pardon me?</p> <p>12 I am asking you to look at Exhibit No. 10, Page 11.</p> <p>13 A Right.</p> <p>14 Q Right-hand column.</p> <p>15 A Right.</p> <p>16 Q That sentence does not say anything about "and/or</p> <p>17 unpublished," does it?</p> <p>18 A Right-- yes, it doesn't.</p> <p>19 Q And then in that sentence, if you go back to Page 22 of</p> <p>20 your report, after you added "and/or unpublished</p> <p>21 epidemiological studies," you took out some information,</p> <p>22 did you not, some words?</p> <p>23 A What are you referring to that I took out?</p> <p>24 Q Well, the words that you took out were, dash, "Usually</p> <p>25 prospective cohort studies," dash, right?</p>

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<p>1 Actually, you also took out the words "of a similar 2 type," so let me restate the question. 3 In your report you took out the words "of a similar 4 type - usually prospective cohort studies"-- and I will 5 put a closed quote there. 6 You took those words out, right? 7 A So, again, I can't remember every place-- because when I 8 write projects, I do take sections from things that I've 9 previously been involved with, since I'm considered on 10 this panel and it's considered as something I'm involved 11 with. I should have cited it, but I would be citing 12 something that I'm part of. 13 This-- it's not true that pooled analyses is only 14 prospective cohort studies, and it is not even true that 15 it's usually. 16 Many pooled analyses of case-control studies-- there 17 are many pulled analyses of clinical trials, so when 18 they're saying, "usually prospective cohort studies," 19 they're referring for what they usually-- for their data 20 or WCRF data, are usually prospective for the nutrition 21 variables, so that's what they specified there. 22 Q The words "of a similar type - usually prospective cohort 23 studies," do not appear in your report. 24 Can we agree on that? 25 MS. PARFITT: Objection; form.</p>	<p>1 studies, but you changed that language for your 2 litigation report to include "unpublished studies," 3 right? 4 MS. PARFITT: Objection; form. 5 THE WITNESS: The Continuous Update 6 Project did make a decision to use only published data 7 because it did not have the personal power to get 8 unpublished. 9 It is typical in pooled analysis and sometimes in 10 meta-analyses to look for additional data if it's known 11 to exist, even if it's not published. 12 This is true for clinical trial pooled analyses, 13 case-control pooled analyses, and cohort pulled analyses. 14 It is not surprising at all that-- it was not 15 unusual to see that in the Terry pooled analysis there 16 were three studies that were previously unpublished that 17 were added to the published data for that pooled 18 analysis. 19 I've seen this for one of the pooled analyses we 20 relied on for the physical activity guidelines committee, 21 and so it's a common method. 22 As long as you use the same criteria to determine if 23 that study has valid data, then it's quite customary to 24 include it in a pooled analysis. 25 Q (By Mr. Williams) The only pooled analysis that you</p>
Page 143	Page 145
<p>1 THE WITNESS: It wouldn't be relevant 2 because I am talking generally about pooled analysis, and 3 it's individual data from-- it could be any type of 4 studies. 5 I mentioned it could be clinical trials. There are 6 many pooled analyses of clinical trials. 7 It could be cohort studies, it could be case-control 8 studies. 9 And sometimes the cohorts and case-control studies 10 will be combined together where the cohort studies are 11 nested case-control studies, so it could be a combination 12 of two different types. 13 MR. WILLIAMS: I move to strike that 14 as nonresponsive. 15 Q (By Mr. Williams) Doctor, my question is this: 16 The words "of a similar type - usually prospective 17 cohort studies," those words do not appear in your 18 report. 19 Can we agree on that? 20 MS. PARFITT: Objection; form, asked 21 and answered. 22 THE WITNESS: I agree they don't 23 appear in my report. 24 Q (By Mr. Williams) So the Continuous Update Project 25 document stated that you should only pool published</p>	<p>1 looked at for this litigation was Terry 2013, correct? 2 MS. PARFITT: Objection; form. 3 THE WITNESS: It's the only one that 4 characterizes a pooled analysis. 5 There were some of the case-control studies that 6 added together more than one study. 7 The second study of the Nurses' Health Study was a 8 pooled analysis of Nurses' Health cases and New England 9 case-control studies, so that was a pooled study that 10 involved just two sets of studies. 11 Q (By Mr. Williams) The only pooled analysis that you 12 cited in your paragraph on Page 22, referencing Item 39, 13 which I'll represent to you is the Terry 2013 study, the 14 only pooled analysis that you studied in your report on 15 Page 22 is the Terry study, correct? 16 A I cited that singly because it was large enough. 17 My point is that it's large enough to be able to 18 look at some of these associations. 19 Q And that Terry 2013 study pooled eight case-control 20 studies, correct? 21 A That's correct. 22 It's a pooling project that has been done for many 23 other variables as well. 24 Q Doctor, we will be here all day and it will go late into 25 the night.</p>

<p style="text-align: right;">Page 146</p> <p>1 I would ask you to answer just the question that I</p> <p>2 ask.</p> <p>3 The question that I'm asking you now is:</p> <p>4 The Terry 2013 pooled eight case-control studies,</p> <p>5 correct?</p> <p>6 That's all I'm asking.</p> <p>7 A That's correct.</p> <p>8 Q You deviated from the Continuous Update Project's</p> <p>9 definition of a pooled analysis, which is on Page 11 of</p> <p>10 Exhibit No. 10, in order to accommodate a study that you</p> <p>11 found helpful for the plaintiffs in this case, correct?</p> <p>12 MS. PARFITT: Objection; form,</p> <p>13 completely misstates her testimony and her opinions.</p> <p>14 You may answer.</p> <p>15 THE WITNESS: The Continuous Update</p> <p>16 Project definition was discussing studies related to</p> <p>17 nutrition, and the Continuous Update Project decided to</p> <p>18 only look at cohort studies for some of the relationships</p> <p>19 they were addressing.</p> <p>20 I believe this is why this sentence was written in</p> <p>21 that way, but it is not true that pooled analyses are</p> <p>22 usually prospective cohorts.</p> <p>23 If you look at pooled analyses in general, many of</p> <p>24 them are clinical trials, they are done in the treatment</p> <p>25 area, many of them are case-control studies, and many can</p>	<p style="text-align: right;">Page 148</p> <p>1 A That's correct.</p> <p>2 Q My question to you then is:</p> <p>3 Can you point us to any reference material anywhere</p> <p>4 that uses word for word the formulation for pooled</p> <p>5 analyses that you have set forth in the first two</p> <p>6 sentences of that paragraph?</p> <p>7 A So I think you're asking about pooled analyses that</p> <p>8 include studies that are not published; is that correct?</p> <p>9 Q I am asking the question that I asked.</p> <p>10 I will restate it one more time.</p> <p>11 Can you point us--</p> <p>12 MR. WILLIAMS: Counsel, I would as</p> <p>13 that you not point to anything.</p> <p>14 MS. PARFITT: I am just trying-- there</p> <p>15 is a monitor, for the Ladies and Gentlemen of the Jury,</p> <p>16 in front of the doctor, and I am just reminding her to</p> <p>17 look at the monitor, but you can--</p> <p>18 MR. WILLIAMS: I think that's</p> <p>19 inappropriate.</p> <p>20 Q (By Mr. Williams) But, Doctor, here is my question</p> <p>21 again:</p> <p>22 The first full paragraph on Page 22 describes pooled</p> <p>23 analyses. I'm referring you to the first two sentences</p> <p>24 there-- are you with me so far?</p> <p>25 A Yes.</p>
<p style="text-align: right;">Page 147</p> <p>1 be cohort studies.</p> <p>2 Q (By Mr. Williams) Let me ask my question this way:</p> <p>3 Doctor, could you point us to some learned treatise,</p> <p>4 study, summary of studies that uses the formulation for</p> <p>5 pooled analysis word for word that is set forth on Page</p> <p>6 22 of your report; that is, could you point us to some</p> <p>7 source that says that pooled analyses is a type of</p> <p>8 meta-analysis that includes published and unpublished</p> <p>9 studies and that simultaneously does not reference</p> <p>10 prospective cohort studies?</p> <p>11 Is there something that you can point us to that</p> <p>12 uses the formulation for pooled analysis that you've set</p> <p>13 forth?</p> <p>14 MS. PARFITT: Objection; form.</p> <p>15 THE WITNESS: I'm a little bit</p> <p>16 confused by the question, but--</p> <p>17 Q (By Mr. Williams) Let me stop you there because if</p> <p>18 you're confused, it does me no good.</p> <p>19 I will restate it.</p> <p>20 Your paragraph here on Page 22 has one, and only</p> <p>21 one, citation, and that's to 39, the Terry 2013 study,</p> <p>22 correct?</p> <p>23 A That's correct.</p> <p>24 Q There are no other citations of any sort in that</p> <p>25 paragraph, correct?</p>	<p style="text-align: right;">Page 149</p> <p>1 Q Looking at those sentences word for word, and I mean</p> <p>2 every word in both of those two sentences-- are you still</p> <p>3 with me?</p> <p>4 A Yes.</p> <p>5 Q Okay. Looking at those two sentences, can you point us</p> <p>6 to any reference material that you have reviewed anywhere</p> <p>7 that describes pooled analyses using the words, and I</p> <p>8 mean word for word, as you set it forth here in the first</p> <p>9 two sentences of Paragraph No. 22?</p> <p>10 MS. PARFITT: Objection; form.</p> <p>11 Q (By Mr. Williams) You either can or you can't.</p> <p>12 The answer is yes, the answer is no.</p> <p>13 I just need to know--</p> <p>14 A Since I wrote that sentence, I am not sure where else it</p> <p>15 would be.</p> <p>16 If I was going to cite-- no, I can't.</p> <p>17 I wrote that sentence.</p> <p>18 Q Okay. What we do know is that the description of pooled</p> <p>19 analysis in Exhibit No. 10, which is the World Cancer</p> <p>20 Research Fund "Judging the evidence" document that has,</p> <p>21 on Page 2, a description of how one is to cite to it,</p> <p>22 what we do know is that that document describes pooled</p> <p>23 analysis as including published epidemiological studies</p> <p>24 of a similar type, usually prospective cohort studies,</p> <p>25 right?</p>

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<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: And I disagree with that</p> <p>3 characterization of pooled studies.</p> <p>4 MR. WILLIAMS: Why don't we take a</p> <p>5 lunch break.</p> <p>6 VIDEOGRAPHER: Going off the record.</p> <p>7 The time is 12:40 p.m.</p> <p>8 (Lunch recess 12:40 to 1:21 p.m.)</p> <p>9</p> <p>10 VIDEOGRAPHER: We are going on the</p> <p>11 record at 1:21 p.m.</p> <p>12 This is the start of Media Unit 3.</p> <p>13 Q (By Mr. Williams) Good afternoon, Doctor.</p> <p>14 This morning there have been several occasions when</p> <p>15 I've used the word "ma'am," and I really apologize, and I</p> <p>16 mean no disrespect. I am going to try to use the word</p> <p>17 "Doctor."</p> <p>18 It's just how I was raised, and I apologize, but I</p> <p>19 do understand that that can be disrespectful. I don't</p> <p>20 mean that at all.</p> <p>21 A No problem. Thanks.</p> <p>22 Q In response to several of my questions earlier today</p> <p>23 about the various World Cancer Research Fund and CUP</p> <p>24 reports that we have marked as Exhibits 4, 5, and 10,</p> <p>25 there have been several times when you have made</p>	<p>1 A That's correct.</p> <p>2 Q Now, early menarche or age of first-- a woman first</p> <p>3 having her period is also listed as something that may be</p> <p>4 seen as a cause of ovarian cancer in this paragraph,</p> <p>5 right?</p> <p>6 A Yes.</p> <p>7 Q Can we agree that early menarche, not bearing children,</p> <p>8 and late natural menopause are not related to nutrition,</p> <p>9 physical activity, or diet?</p> <p>10 A This paragraph is related to background, and it's talking</p> <p>11 about menstrual cycles during a woman's lifetime. That's</p> <p>12 why it's talking about all of those variables related to</p> <p>13 early menarche, late menopause.</p> <p>14 I am not sure why whoever wrote this focused in on</p> <p>15 that, on a woman's menstrual cycle.</p> <p>16 They did not do a full systematic review of the risk</p> <p>17 factors for ovarian cancer.</p> <p>18 I can see from what was written here--</p> <p>19 Q Whether you consider it to be a full systematic review or</p> <p>20 not, my question is:</p> <p>21 Early menarche, not bearing children, and late</p> <p>22 natural menopause are not, in and of themselves, related</p> <p>23 to nutrition, physical activity, or diet, right?</p> <p>24 A And the whole report was not-- was to discuss and</p> <p>25 interpret and summarize meta-analyses-- for all of the</p>
Page 151	Page 153
<p>1 reference to your view that the focus of those reports</p> <p>2 was on nutrition, physical activity, and diet.</p> <p>3 Do you recall that that has happened occasionally?</p> <p>4 A Yes.</p> <p>5 Q If you could take out Exhibit No. 5, which is the 2018</p> <p>6 report of the WCRF-- and I will ask you to turn to Page</p> <p>7 8.</p> <p>8 Section 4, "Other established causes," Page 8-- do</p> <p>9 you have that in front of you, ma'am?</p> <p>10 A Yes.</p> <p>11 Q Section No. 4 is entitled, "Other established causes,"</p> <p>12 and let me-- while you have that in front of you, let me</p> <p>13 ask:</p> <p>14 Not bearing children is listed as something that</p> <p>15 this report says may be a cause of ovarian cancer,</p> <p>16 correct?</p> <p>17 A It says, "May be seen as protective against ovarian</p> <p>18 cancer," yes.</p> <p>19 Q Well, actually, it says-- I will just read it. The</p> <p>20 second sentence says, "Not bearing children increases the</p> <p>21 risk of and may be seen as a cause of ovarian cancer,"</p> <p>22 and it goes on to say, "The reverse also applies: Bearing</p> <p>23 children reduces the risk of and may be seen as</p> <p>24 protective against ovarian cancer."</p> <p>25 Do you see that?</p>	<p>1 cancers, different writers put in paragraphs about some</p> <p>2 general factors about the cancers, and there was no</p> <p>3 effort to do a systematic review, so these are not causal</p> <p>4 analyses that were listed here.</p> <p>5 I don't know why these particular ones were picked.</p> <p>6 They're missing some.</p> <p>7 They're missing endometriosis, for example, as well</p> <p>8 as talcum powder.</p> <p>9 They are missing public inflammatory disease, so it</p> <p>10 is not a full review.</p> <p>11 For some reason they picked just some</p> <p>12 menstrual-related variables to mention here.</p> <p>13 Q Now, again, you said, "they."</p> <p>14 Once this draft was prepared, you have testified</p> <p>15 this morning that the panel, on which you are a member,</p> <p>16 reviews and makes judgments based upon the draft that is</p> <p>17 received, right?</p> <p>18 A In-- the 2014 draft.</p> <p>19 To my knowledge it was not changed.</p> <p>20 We did not see another update to review prior to the</p> <p>21 2018 publication of everything together.</p> <p>22 This was a 2014 document and it was on the website</p> <p>23 in 2014.</p> <p>24 Q I want the record to be clear the document that I'm</p> <p>25 referring you to right now, the Exhibit No. 5 to your</p>



<p style="text-align: right;">Page 154</p> <p>1 deposition, is the revised document dated 2018.</p> <p>2 We have that clear, right?</p> <p>3 A Yes, but it also says, "2014" on the label for ovarian</p> <p>4 cancer.</p> <p>5 Q It does, but it also says that it was revised and</p> <p>6 published in 2018, right?</p> <p>7 I don't want to argue with you, but it does say that</p> <p>8 was revised and published in 2018, true?</p> <p>9 MS. PARFITT: Objection; form.</p> <p>10 Q (By Mr. Williams) Go ahead.</p> <p>11 A To my knowledge, the content was not changed.</p> <p>12 I am not sure exactly why it was called "Revised,"</p> <p>13 except that everything was put together and the</p> <p>14 recommendations were added to this obviously, the overall</p> <p>15 cancer recommendations, but to my knowledge the</p> <p>16 meta-analysis for the nutrition variables and all were</p> <p>17 not updated.</p> <p>18 Clearly this review of other potential causes was</p> <p>19 not updated, so in my mind it's the 2014 report.</p> <p>20 Q Now, let me focus you back on the lack of connection</p> <p>21 between early menarche, nutrition, and physical activity,</p> <p>22 and diet, okay?</p> <p>23 Whether you believe this was a complete analysis or</p> <p>24 not, the fact is that this report, which is marked as</p> <p>25 Exhibit No. 5, does discuss menarche, not bearing</p>	<p style="text-align: right;">Page 156</p> <p>1 talc or not using talc is a modifiable behavior.</p> <p>2 If you would, with your answer, as you describe how</p> <p>3 you think these are unrelated and different contexts, how</p> <p>4 is it that those contexts are different for purposes of</p> <p>5 the analysis that you have done in this case?</p> <p>6 MS. PARFITT: Objection; form.</p> <p>7 THE WITNESS: So this is an issue</p> <p>8 about measuring the exposure.</p> <p>9 If you ask about talcum powder product use, you</p> <p>10 typically are asking about something that is used once or</p> <p>11 twice a day.</p> <p>12 Somebody may just use one product. Perhaps they use</p> <p>13 more, but they're not going to be using as many variables</p> <p>14 as in nutrition.</p> <p>15 Assessing nutrition is extremely difficult.</p> <p>16 Assessing nutrition for a lifetime is even more</p> <p>17 difficult, and so this is why for case-control studies</p> <p>18 nutrition analyses are very difficult to do if you are</p> <p>19 trying to ask somebody retrospectively, "What did you eat</p> <p>20 when you were in your 20s?"</p> <p>21 You can ask somebody whether they used some products</p> <p>22 in their 20s and expect their recall to be much better</p> <p>23 than what they ate 30, 40 years ago because we are always</p> <p>24 talking about decades of latency between exposure and</p> <p>25 development of ovarian cancer.</p>
<p style="text-align: right;">Page 155</p> <p>1 children, and late menopause, right?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: It does include those,</p> <p>4 and it's missing other risk factors for ovarian cancer.</p> <p>5 Q (By Mr. Williams) So the statement "Epidemiological</p> <p>6 principles" in this report, and those that we looked at</p> <p>7 in other exhibits, Exhibit 4 and Exhibit No. 10, do apply</p> <p>8 to your analysis of talc and ovarian cancer in this case,</p> <p>9 right?</p> <p>10 They do apply to things that are not limited to</p> <p>11 nutrition, physical activity, and diet, correct?</p> <p>12 MS. PARFITT: Objection; form,</p> <p>13 misstates her testimony.</p> <p>14 THE WITNESS: I am curious, what is</p> <p>15 the statement "epidemiologic principles"? Are you</p> <p>16 referring to something in this ovarian cancer report?</p> <p>17 Q (By Mr. Williams) Let me ask it this way:</p> <p>18 Why is it that nutrition is a totally separate</p> <p>19 context than talc?</p> <p>20 Explain, if you would, to the Court, who is the</p> <p>21 person who is going to review this-- describe to the</p> <p>22 Court how nutrition is a separate context than talc, with</p> <p>23 particular attention, Dr. McTiernan, to the notion that</p> <p>24 nutrition, what someone eats and takes into their body,</p> <p>25 is a modifiable behavior in the same manner that using</p>	<p style="text-align: right;">Page 157</p> <p>1 Case-control studies can be done for numbers of</p> <p>2 exposures, and they can be-- characterize exposure very</p> <p>3 well, but nutrition is a special case.</p> <p>4 Some epidemiologists still do do case-control</p> <p>5 studies of nutrition, but some, like-- because there are</p> <p>6 so many cohort studies available in nutrition, some</p> <p>7 epidemiologists prefer to look at that, especially when</p> <p>8 you're looking at a cancer that has a long latency</p> <p>9 period, and so you are looking for long interval between</p> <p>10 when the exposure happened and when the cancer occurred.</p> <p>11 Q (By Mr. Williams) Have you completed your answer?</p> <p>12 A Pardon me?</p> <p>13 Q Have you completed your answer?</p> <p>14 A Yes.</p> <p>15 Q Anything else that you want to add about the differences</p> <p>16 between the context of nutritional and dietary concerns</p> <p>17 versus the use of talcum powder?</p> <p>18 A I think that's it.</p> <p>19 Q Okay. Why is it harder to remember-- strike that.</p> <p>20 Why would it be harder for me or anyone else to</p> <p>21 remember the types of foods I ate in my teens or my 20s</p> <p>22 as compared to whether I used talcum powder during a</p> <p>23 particular time in my life?</p> <p>24 A When you ask people about nutrition, you don't just ask</p> <p>25 one question, "How often did you eat beef?"</p>



<p style="text-align: right;">Page 158</p> <p>1 You are asking them for multiple types of foods, how</p> <p>2 often they ate it, how much they ate it.</p> <p>3 We often use food frequency questionnaires that can</p> <p>4 be 12 pages long, each with about 20 to 30 items on them,</p> <p>5 and to ask about-- somebody to recall that much</p> <p>6 information retrospectively is more difficult than to ask</p> <p>7 them to recall using one item.</p> <p>8 Medications, we can often get information</p> <p>9 retrospectively, like hormone therapy. We can ask that</p> <p>10 about that case-control studies and help the woman</p> <p>11 remember, but because it was one pill that the woman had</p> <p>12 to take per day, it is an easier thing to remember than</p> <p>13 50 to 100 variables that you have to remember with a</p> <p>14 dietary recall.</p> <p>15 Q Do you think it would be easier for a woman to recall</p> <p>16 that she used talcum powder during her 20s than it would</p> <p>17 be for her to recall that she ate red meat in her 20s?</p> <p>18 A I think it would be easier in the sense that people are</p> <p>19 going to remember something that intimate, how often--</p> <p>20 whether they used it or not, and we don't ask people just</p> <p>21 one question, "Did you eat red meat?"</p> <p>22 We ask them hundreds of questions of what they ate.</p> <p>23 Q Do you ask hundreds of questions about red meat?</p> <p>24 A We don't usually do studies with just red meat.</p> <p>25 We do studies where we are asking about entire</p>	<p style="text-align: right;">Page 160</p> <p>1 THE WITNESS: I think if you wanted to</p> <p>2 see if-- if you had just that one question, what somebody</p> <p>3 ate, what meat they ate, a case-control study would be</p> <p>4 just fine, you could ask somebody what they ate in the</p> <p>5 past if it's just one variable.</p> <p>6 If you're asking them to remember 50 to 100</p> <p>7 variables, it's much more difficult.</p> <p>8 Q (By Mr. Williams) Have we exhausted all of the reasons</p> <p>9 why you believe that the context of this Exhibit No. 5,</p> <p>10 this CUP update, is totally different, as you said, than</p> <p>11 the context of the talc-related studies?</p> <p>12 Is there anything else that you need to add to your</p> <p>13 answer?</p> <p>14 A I can't think of anything.</p> <p>15 Q Pardon me?</p> <p>16 A I can't think of anything, no.</p> <p>17 Q Let me change topics slightly.</p> <p>18 As an epidemiologist, you are familiar with a type</p> <p>19 of bias called confounding, right?</p> <p>20 A Yes.</p> <p>21 Q Confounding is a type of bias that occurs when a third</p> <p>22 variable interferes with a true relationship between an</p> <p>23 exposure and an outcome, right?</p> <p>24 A Yes.</p> <p>25 Q Those are the words you used in your report, right?</p>
<p style="text-align: right;">Page 159</p> <p>1 dietary pattern.</p> <p>2 I don't know of any study that asks just that one</p> <p>3 question.</p> <p>4 Q These studies that relate to talcum powder refer often to</p> <p>5 multiple products and substances that a person puts on or</p> <p>6 in her body; do they not?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 THE WITNESS: From the questionnaires</p> <p>9 that I've looked at from these studies, when they're</p> <p>10 available, they are much simpler questions, and often</p> <p>11 they were assisted with remembering by in-person</p> <p>12 interview or telephone interview with someone that is</p> <p>13 helping them remember what they did during that period of</p> <p>14 life.</p> <p>15 That can be used for a simple question, simple</p> <p>16 exposure.</p> <p>17 For diet, it's much more difficult.</p> <p>18 Q (By Mr. Williams) I understand that some questionnaires</p> <p>19 may be longer than others, but with respect to an</p> <p>20 individual question, that is whether someone ate red meat</p> <p>21 in their 20s or someone used talcum powder in their 20s,</p> <p>22 do you really see those questions as-- one of those</p> <p>23 questions as more complicated than the other, taken</p> <p>24 individually?</p> <p>25 MS. PARFITT: Objection to the form.</p>	<p style="text-align: right;">Page 161</p> <p>1 A Mm-hm.</p> <p>2 Q "Yes"?</p> <p>3 A Yes.</p> <p>4 Q A confounder is one that is related both to the risk</p> <p>5 disease and to the exposure, correct?</p> <p>6 A That's correct.</p> <p>7 Q The classic example that you use in your report is people</p> <p>8 who carry matches are more likely to develop lung cancer</p> <p>9 than individuals who do not carry matches, right?</p> <p>10 A Correct.</p> <p>11 Q In that example, the cause and effect relationship, the</p> <p>12 true one, is not between matches and lung cancer, but</p> <p>13 rather between smoking and lung cancer, correct?</p> <p>14 A Correct.</p> <p>15 Q Correlation does not equal causation, correct?</p> <p>16 The two do not equate?</p> <p>17 A I wouldn't go from one to the other, so-- this just means</p> <p>18 that there's another variable explaining an association</p> <p>19 in the first example, which is confounding.</p> <p>20 Q Do you believe that correlation and causation mean one in</p> <p>21 the same thing when you are dealing with epidemiological</p> <p>22 studies?</p> <p>23 A I don't usually use the word "correlation."</p> <p>24 Association is one thing we look at when we're</p> <p>25 trying to determine if there's a causal relationship.</p>

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<p>1 Q What I'm juxtaposing is correlation on the one hand and</p> <p>2 causation on the other.</p> <p>3 Do you have my question in mind?</p> <p>4 A I see it here, yes.</p> <p>5 Q Do you believe that correlation is identical to</p> <p>6 causation?</p> <p>7 MS. PARFITT: Objection; asked and</p> <p>8 answered.</p> <p>9 THE WITNESS: I think by "correlation"</p> <p>10 you mean "association."</p> <p>11 Q (By Mr. Williams) I mean a correlation between two</p> <p>12 variables.</p> <p>13 MS. PARFITT: Objection; form.</p> <p>14 THE WITNESS: Yeah, I think</p> <p>15 correlation is one way that two variables can be related,</p> <p>16 and causation is a much more complicated analysis.</p> <p>17 Q (By Mr. Williams) Same question with respect to</p> <p>18 association.</p> <p>19 Does association equate with causation?</p> <p>20 A I would say the same thing, association is part of causal</p> <p>21 analysis.</p> <p>22 Q So in a paper studying the association between</p> <p>23 match-carrying, for example, and lung cancer, you would</p> <p>24 need to adjust for smoking before making any conclusions</p> <p>25 about the risk estimates, true?</p>	<p>1 that Counsel gave you and produced to us on January 25th,</p> <p>2 a few days ago.</p> <p>3 Do you see that on the list?</p> <p>4 A No.</p> <p>5 Which list is this?</p> <p>6 MS. PARFITT: If I may, Counsel, I</p> <p>7 will hand her Exhibit No. 3.</p> <p>8 THE WITNESS: Oh, Kesmodel?</p> <p>9 MR. WILLIAMS: Yes.</p> <p>10 THE WITNESS: Yes.</p> <p>11 Q (By Mr. Williams) So Kesmodel is one of the studies that</p> <p>12 was provided to us, Defense counsel, by Plaintiffs'</p> <p>13 counsel on January 25th, correct?</p> <p>14 A Is that the date?</p> <p>15 Q That's the date we received it. I will represent that to</p> <p>16 you.</p> <p>17 A Okay.</p> <p>18 Q Have you read that study?</p> <p>19 A Yes.</p> <p>20 Q We'll mark that as Exhibit No. 12.</p> <p>21 (Exhibit No. 12 marked</p> <p>22 for identification.)</p> <p>23 ////</p> <p>24 Q (By Mr. Williams) I will just refer you quickly to the</p> <p>25 abstract on the first page of Exhibit No. 12, the</p>
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<p>1 A I think usually we would want to look at it the other</p> <p>2 way.</p> <p>3 If you're looking at-- you wouldn't adjust for it</p> <p>4 necessarily. You might make sure to be aware that it's</p> <p>5 part of the causal-- part of the pathway.</p> <p>6 If you totally adjust for it, then it might make the</p> <p>7 relationship disappear, so perhaps it's not the best</p> <p>8 explanatory variable to use-- the best example, but the</p> <p>9 premise is that there can be a second variable that can</p> <p>10 be interfering with the relationship, which is why we</p> <p>11 adjust for things that can potentially be related to both</p> <p>12 the exposure and to the disease.</p> <p>13 Q And the second variable in the example that I used and</p> <p>14 that you used in your report was that variable of whether</p> <p>15 someone smokes?</p> <p>16 A Yes.</p> <p>17 Q In addition to the variable of their having matches</p> <p>18 often, right?</p> <p>19 A Yes.</p> <p>20 Q And one of the studies that you gave us this morning is a</p> <p>21 study written by Ulrik, U-L-R-I-K S. Kesmodel,</p> <p>22 K-E-S-M-O-D-E-L.</p> <p>23 Do you remember giving that one to us this morning?</p> <p>24 A Is this in the list?</p> <p>25 Q It was in the-- I'm sorry, it was identified on the list</p>	<p>1 Kesmodel study.</p> <p>2 About three-quarters of the way down, the abstract</p> <p>3 paragraph, it says, "Misclassification of confounders is</p> <p>4 an issue that needs special attention by researchers, as</p> <p>5 failure to measure accurately one or more strong</p> <p>6 confounders may seriously bias the observed results."</p> <p>7 Did I read that correctly from the abstract?</p> <p>8 A Yes.</p> <p>9 Q In the case of talcum powder use and the epidemiological</p> <p>10 studies that you've reviewed, a confounder is one that is</p> <p>11 related to ovarian cancer and perineal talc use, correct?</p> <p>12 A Correct, within that data set, yes.</p> <p>13 Q You agree that high body mass index, or BMI, is an</p> <p>14 established risk factor for ovarian cancer, true?</p> <p>15 A It is a risk factor, yes.</p> <p>16 Q And the WCRF document that we looked at this morning,</p> <p>17 that actually said that body mass index is probably a</p> <p>18 cause of ovarian cancer.</p> <p>19 Do you remember that this morning?</p> <p>20 MS. PARFITT: Objection.</p> <p>21 THE WITNESS: Yes.</p> <p>22 Q (By Mr. Williams) Body mass index is a measure of weight</p> <p>23 as compared to a measurement of height, right?</p> <p>24 A Yes.</p> <p>25 Q Now, the Continuous Update Project, for which you served</p>

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<p>1 as a panel member, has actually concluded that body mass</p> <p>2 index is a probable cause.</p> <p>3 That was Exhibit No.-- I believe it was Exhibit</p> <p>4 No. 5 from this morning.</p> <p>5 Do you remember that?</p> <p>6 A I believe so.</p> <p>7 Yes.</p> <p>8 Q In May 2018, after you were hired by Plaintiffs' lawyers</p> <p>9 in the talc litigation, you wrote an article concluding</p> <p>10 that there was strong evidence that being overweight or</p> <p>11 obese increased the risk for cancers.</p> <p>12 Do you remember that?</p> <p>13 That was Exhibit No. 9 that we talked about this</p> <p>14 morning.</p> <p>15 MS. PARFITT: Sorry, Exhibit No. 9?</p> <p>16 MR. WILLIAMS: Yes.</p> <p>17 THE WITNESS: The article--</p> <p>18 Q (By Mr. Williams) The article that had your picture on</p> <p>19 it this morning, Exhibit No. 9 that we showed you--</p> <p>20 A Oh, press--</p> <p>21 Q It's 9.</p> <p>22 On the second page in the first paragraph it says</p> <p>23 that the latest report found strong evidence that being</p> <p>24 overweight or obese increased the risk for a number of</p> <p>25 things, and one of the things that is mentioned is cancer</p>	<p>1 A Yes.</p> <p>2 Q Let me direct you to Page 250, which should be the second</p> <p>3 page of the copy that was handed to you, the left-hand</p> <p>4 column, first paragraph, last sentence-- hold on. I am</p> <p>5 trying to find the citation.</p> <p>6 Under the results section on that page, Page 250, do</p> <p>7 you see that first paragraph?</p> <p>8 A Yes.</p> <p>9 Q The last sentence there says, "Talc use was associated</p> <p>10 with higher body mass index and inversely associated with</p> <p>11 current cigarette smoking."</p> <p>12 Do you see that?</p> <p>13 A Yes.</p> <p>14 Q Talc use, this study found, was associated with higher</p> <p>15 body mass index, true?</p> <p>16 That's what it says?</p> <p>17 A It doesn't give us any statistics on it, but if you look</p> <p>18 at the table, you can see a slight association, yes.</p> <p>19 Q Well, Table No. 1 does give us some information, correct?</p> <p>20 MS. PARFITT: Objection; form.</p> <p>21 THE WITNESS: It doesn't give us any P</p> <p>22 values of how different it was. It doesn't give us</p> <p>23 percents, but-- yeah.</p> <p>24 Q (By Mr. Williams) Okay. And do you remember that in the</p> <p>25 Cramer 1999 paper, that you rely upon, said that</p>
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<p>1 of the ovary, right?</p> <p>2 MS. PARFITT: Objection.</p> <p>3 THE WITNESS: Yes.</p> <p>4 Q (By Mr. Williams) Okay. Talc use is associated with</p> <p>5 higher body mass index, true?</p> <p>6 A I have not investigated that.</p> <p>7 I did not do a review on body mass index and talc</p> <p>8 use.</p> <p>9 Q The observation that talc use is associated with higher</p> <p>10 body mass index is something that was noted in many of</p> <p>11 the studies that you reviewed for purposes of your work,</p> <p>12 right?</p> <p>13 MS. PARFITT: Objection.</p> <p>14 THE WITNESS: I didn't focus on body</p> <p>15 mass index and talc use.</p> <p>16 Q (By Mr. Williams) Let me ask--</p> <p>17 A If you have something to point to, we can look at it.</p> <p>18 Q Let's look at the Gertig 2000 study. We have talked</p> <p>19 about that one today.</p> <p>20 This is going to be Exhibit No. 13.</p> <p>21 (Exhibit No. 13 marked</p> <p>22 for identification.)</p> <p>23 ////</p> <p>24 Q (By Mr. Williams) Do you have the Gertig study in front</p> <p>25 of you, what we have marked as Exhibit No. 13?</p>	<p>1 characteristics, such as body odor or excessive</p> <p>2 perspiration, might predispose to both talc use and</p> <p>3 ovarian cancer, but adjusting for BMI should control for</p> <p>4 those effects.</p> <p>5 Do you remember that?</p> <p>6 MS. PARFITT: Counsel, do you have a</p> <p>7 copy of Cramer 1999 or could we get that?</p> <p>8 MR. WILLIAMS: I am just asking if she</p> <p>9 remembers it now, and if she doesn't--</p> <p>10 THE WITNESS: I don't recall. I would</p> <p>11 have to look at it.</p> <p>12 (Exhibit No. 14 marked</p> <p>13 for identification.)</p> <p>14</p> <p>15 Q (By Mr. Williams) We will mark the Cramer 1999 study as</p> <p>16 Exhibit No. 14.</p> <p>17 I will direct your attention to the page that has in</p> <p>18 the upper right-hand corner "355," the left-hand column,</p> <p>19 second paragraph, the one that begins with, "Regarding</p> <p>20 potential."</p> <p>21 About midway down that paragraph it says,</p> <p>22 "Characteristics such as body odor or excessive</p> <p>23 perspiration might represent subtle constitutional</p> <p>24 features that might predispose to both talc use and</p> <p>25 ovarian cancer, but adjusting for BMI should control for</p>

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<p>1 these effects."</p> <p>2 Do you see that?</p> <p>3 A Yes.</p> <p>4 Q Does it make sense to you, separate and apart from these</p> <p>5 studies that I've shown you, that people who use talc on</p> <p>6 their bodies, including people who use talc in their</p> <p>7 perineal area, do so to absorb sweat and other moisture?</p> <p>8 A I didn't do a survey of why people use this.</p> <p>9 It's not clear that only people who sweat and have</p> <p>10 body odor are choosing to use body powders, so this isn't</p> <p>11 a substantiated sentence.</p> <p>12 I'm not quite clear.</p> <p>13 One statement it has about-- that it may predispose</p> <p>14 to ovarian cancer, I don't know of any literature</p> <p>15 associating body odor or perspiration for risk of or even</p> <p>16 early diagnosis of ovarian cancer, so I'm confused by</p> <p>17 that.</p> <p>18 Q Well, let me ask you to make an assumption then.</p> <p>19 If you make an assumption for me that BMI increases</p> <p>20 the risk for ovarian cancer, and you further make the</p> <p>21 assumption that more talc users have high BMI than</p> <p>22 nontalc users, do you believe that studies looking at</p> <p>23 talc and ovarian cancer should adjust for BMI?</p> <p>24 MS. PARFITT: Objection; form,</p> <p>25 misstates the evidence.</p>	<p>1 multivariate adjusted.</p> <p>2 If it was confounding from any of these variables</p> <p>3 that they adjusted for, you would see very big</p> <p>4 differences or much more marked than you see between</p> <p>5 age-adjusted relative risk and multivariate adjusted</p> <p>6 relative risk.</p> <p>7 Q Now, have you done the analysis to determine whether or</p> <p>8 not BMI was associated with greater talc use or whether</p> <p>9 BMI was associated as a confounder in terms of causing a</p> <p>10 higher odds ratio or risk ratio in the Gertig study?</p> <p>11 A Did I personally do any statistics on these? I didn't</p> <p>12 have the data to do the statistics, but you can see that</p> <p>13 its multivariate relative risk is so similar to</p> <p>14 age-adjusted relative risk. That means that it is not</p> <p>15 confounding in the data.</p> <p>16 Q Did you do that analysis as part of your work?</p> <p>17 MS. PARFITT: Objection; asked and</p> <p>18 answered.</p> <p>19 THE WITNESS: I am doing it right now.</p> <p>20 Q (By Mr. Williams) Did you--</p> <p>21 A Since you pointed it out.</p> <p>22 Q Did you do that analysis as part of your work--</p> <p>23 A When I presented relative risk, I tended to present the</p> <p>24 most adjusted relative risk I could find, I believe.</p> <p>25 That's what I tried to do.</p>
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<p>1 THE WITNESS: So we see in one study--</p> <p>2 I did not do a full review of all these studies, and I</p> <p>3 don't believe the data was available in all of them the</p> <p>4 way the Nurses' Health Study presented, which showed body</p> <p>5 mass index-- in all of the studies, and I didn't do a</p> <p>6 survey to look at the association between body mass index</p> <p>7 and talc use.</p> <p>8 I can see from these data in the Gertig study that</p> <p>9 it wasn't a confounder.</p> <p>10 They adjusted for it, but if you look at Table No. 2</p> <p>11 in the Gertig paper, the age-adjusted relative risk is</p> <p>12 very similar to the multivariate adjusted relative risk.</p> <p>13 The multivariate adjusted relative risk included</p> <p>14 body mass index, so this tells me that it's unlikely to</p> <p>15 be any or extremely little confounding when you see such</p> <p>16 a similar result for age-adjusted relative risk as you do</p> <p>17 for multivariate relative risk.</p> <p>18 Q Just so we are clear, you are looking right now at</p> <p>19 Exhibit No. 13, the Gertig study?</p> <p>20 A Sorry. Yes.</p> <p>21 Q Table No. 1 on Page 250, correct?</p> <p>22 A Table 1 and Table 2.</p> <p>23 Table 1 shows the association of BMI versus talc</p> <p>24 use.</p> <p>25 Table 2 shows the relative risk, age adjusted and</p>	<p>1 Q You reviewed three cohort studies in connection with your</p> <p>2 report, according to you, because you count Gates 2008</p> <p>3 and Gates 2010 as part of Gertig, correct? So that</p> <p>4 counts as one, right?</p> <p>5 A I believe those cases-- those two other cases that were</p> <p>6 in the second-- you are talking about the second Nurses'</p> <p>7 Health Study, the Gates 2008? I believe those 2010 were</p> <p>8 in the first one, but they're never quite clear.</p> <p>9 Q Let me start over.</p> <p>10 A Sorry.</p> <p>11 Q I don't want to quibble with you.</p> <p>12 You reviewed Gertig 2000, Houghton 2014, and</p> <p>13 Gonzalez 2016, correct?</p> <p>14 A That's correct.</p> <p>15 Q You also reviewed Gates 2008 and Gates 2010, correct?</p> <p>16 A Correct.</p> <p>17 Q Each one of those studies found no overall statistically</p> <p>18 significant association between perineal talc use and</p> <p>19 ovarian cancer?</p> <p>20 MS. PARFITT: Objection.</p> <p>21 Q (By Mr. Williams) I am not asking about serous invasive,</p> <p>22 as you went to before.</p> <p>23 I am talking about overall perineal task use.</p> <p>24 MS. PARFITT: Objection.</p> <p>25 Q (By Mr. Williams) Correct?</p>

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<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: And the sample sizes</p> <p>3 were too small to be able to determine statistical</p> <p>4 significance with that level of relative risk.</p> <p>5 Q (By Mr. Williams) It was a consistent finding of those</p> <p>6 cohort studies that there was not a statistically</p> <p>7 significant association between perineal talc use overall</p> <p>8 and ovarian cancer, right?</p> <p>9 MS. PARFITT: Objection; form, asked</p> <p>10 and answered.</p> <p>11 THE WITNESS: The studies were not</p> <p>12 large enough.</p> <p>13 There were not enough cases to determine statistical</p> <p>14 significance or to have a statistically significant</p> <p>15 result.</p> <p>16 Q (By Mr. Williams) Is it your testimony that those</p> <p>17 studies found a statistically significant association</p> <p>18 overall between perineal talc use and ovarian cancer?</p> <p>19 MS. PARFITT: Objection; form.</p> <p>20 Counsel, that has been asked now about three or four</p> <p>21 times.</p> <p>22 I think she has given an answer.</p> <p>23 I know you don't like it, but she has responded.</p> <p>24 Q (By Mr. Williams) Are you saying that those studies</p> <p>25 found a statistically significant association between</p>	<p>1 able to tell us, as you sit here, how many of the</p> <p>2 case-control studies that you read and reviewed and are</p> <p>3 relying on in this case do not adjust for body mass</p> <p>4 index?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: No, I did not count</p> <p>7 that.</p> <p>8 Q (By Mr. Williams) Why not?</p> <p>9 MS. PARFITT: I'm sorry, what was the</p> <p>10 question?</p> <p>11 Q (By Mr. Williams) Why not?</p> <p>12 MS. PARFITT: Objection.</p> <p>13 THE WITNESS: I was tasked to look at</p> <p>14 the overall association.</p> <p>15 I did not look at specific confounders for each of</p> <p>16 the studies.</p> <p>17 Q (By Mr. Williams) So if there were a confounder that</p> <p>18 could impact the answer to the question of whether</p> <p>19 perineal use of talcum powder causes cancer, you didn't</p> <p>20 look at it?</p> <p>21 MS. PARFITT: Objection; form,</p> <p>22 misstates the testimony.</p> <p>23 THE WITNESS: There could be</p> <p>24 confounding variables in any type of research that may or</p> <p>25 may not be available.</p>
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<p>1 perineal talc use and ovarian cancer?</p> <p>2 MS. PARFITT: Objection, form.</p> <p>3 Again, a fifth time asked and answered.</p> <p>4 THE WITNESS: I am saying that they</p> <p>5 did not have a large enough sample size to find a</p> <p>6 statistically significant association.</p> <p>7 Q (By Mr. Williams) Identify for us on the record any</p> <p>8 cohort study that concluded that there was a</p> <p>9 statistically significant overall association between</p> <p>10 talc and ovarian cancer.</p> <p>11 A I can't identify any.</p> <p>12 Q In forming your opinions in this litigation, did you take</p> <p>13 note of the fact that each of those cohort studies</p> <p>14 accounted for body mass index or BMI?</p> <p>15 A I believe I did not go through specific-- I am sure I</p> <p>16 didn't go through specific confounding variables.</p> <p>17 I just noted that they adjusted for potential</p> <p>18 confounders and presented the most adjusted variable.</p> <p>19 Q Your written report does not take note of the fact that</p> <p>20 each of the cohort studies you reviewed accounted for</p> <p>21 body mass index, did it?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 THE WITNESS: No, I didn't note one</p> <p>24 particular variable for adjustment.</p> <p>25 Q (By Mr. Williams) Without reviewing the studies, are you</p>	<p>1 I noticed in the Gertig study, the data that we just</p> <p>2 talked about, that body mass index was not a confounder,</p> <p>3 so that gives me some-- at least in one data set, that it</p> <p>4 wasn't an issue, nor would the other variables adjusted</p> <p>5 for have been confounders because the multivariate</p> <p>6 relative risk is so similar to the age-adjusted relative</p> <p>7 risk.</p> <p>8 Q (By Mr. Williams) Did the Gertig study conclude what you</p> <p>9 just said?</p> <p>10 A I think I just presented it.</p> <p>11 Q While you are reading, Doctor, I just want to be clear</p> <p>12 with what my question is.</p> <p>13 My question is:</p> <p>14 Did-- strike that.</p> <p>15 Where in the Gertig study did the Gertig study say</p> <p>16 or conclude that BMI is not a confounder for talc use?</p> <p>17 A It's a general epidemiologic principle that if you see</p> <p>18 similar results for the multivariate relative risk that</p> <p>19 you see with just a-- either an unadjusted or in this</p> <p>20 case age-adjusted relative risk, that the confounding</p> <p>21 variables that were adjusted for in the multivariate are</p> <p>22 unlikely to be confounders.</p> <p>23 If they were, the data would look different.</p> <p>24 Q Have you completed your answer?</p> <p>25 A Yes.</p>



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<p>1 Q Did the Gertig study expressly state that BMI is not a</p> <p>2 confounder for talc?</p> <p>3 MS. PARFITT: Objection; asked and</p> <p>4 answered.</p> <p>5 THE WITNESS: I don't see that they</p> <p>6 said that, but the data are showing it to me.</p> <p>7 Q (By Mr. Williams) In forming your opinions in this</p> <p>8 litigation, you did not do any analysis of whether the</p> <p>9 studies that you relied upon adjusted for body mass</p> <p>10 index, correct?</p> <p>11 A I didn't enumerate that, no.</p> <p>12 Q I would like to ask you about another type of study, the</p> <p>13 meta and the pooled analyses.</p> <p>14 You rely significantly on those study types,</p> <p>15 correct?</p> <p>16 A That's correct.</p> <p>17 Q For the meta and the pooled analysis, the ones with the</p> <p>18 combined data, you believe that the summary relative</p> <p>19 risks for any talc use versus no talc use were</p> <p>20 consistent, true?</p> <p>21 A Yes, I want to look at the--</p> <p>22 Q For reference, in your report, Exhibit No. 2 at Page 56.</p> <p>23 A I want to look at the papers too.</p> <p>24 Q I am just asking about your report, not the papers yet.</p> <p>25 As far as your report is concerned, you believe that</p>	<p>1 case-control studies, the eight case-control studies,</p> <p>2 plus three previous and published studies.</p> <p>3 Q You did not perform your own meta-analysis, right?</p> <p>4 A No, I didn't.</p> <p>5 Q One of the reasons you did not perform your own</p> <p>6 meta-analysis was because you believe that there were</p> <p>7 two, in your words, excellent meta-analyses that had</p> <p>8 recently been published, Penninkilampi and Berge,</p> <p>9 correct?</p> <p>10 A Correct.</p> <p>11 Q "Penninkilampi" is spelled P-E-N-N-I-N-K-I-L-A-M-P-I.</p> <p>12 That was from 2018, correct?</p> <p>13 A Yes.</p> <p>14 Q And the Berge analysis, B-E-R-G-E, was from 2017?</p> <p>15 A Yes.</p> <p>16 Q You believe that those two studies are consistent with</p> <p>17 one another?</p> <p>18 A Yes, they have very similar results.</p> <p>19 Q Do you believe they support your opinion in the case that</p> <p>20 perineal talcum powder can cause ovarian cancer?</p> <p>21 A Yes.</p> <p>22 Q Let me show you the Penninkilampi study. We'll mark it</p> <p>23 as Exhibit No. 15, I believe.</p> <p>24 (Exhibit No. 15 marked</p> <p>25 for identification.)</p>
Page 179	Page 181
<p>1 the summary of relative risks for any talc use versus no</p> <p>2 talc use are consistent, right?</p> <p>3 A And where are you, Page 56?</p> <p>4 Q Page 56, the top paragraph, middle of the paragraph,</p> <p>5 sentence starting with, "The summary relative risks,"</p> <p>6 about four lines down.</p> <p>7 A "Were quite consistent," yes, I wrote that.</p> <p>8 Q Are there other ways in which the meta and the pooled</p> <p>9 analyses are consistent, in your opinion?</p> <p>10 A I am not sure what you're asking.</p> <p>11 Q Well, in addition to the notion that the relative risks</p> <p>12 were quite consistent, in your opinion, across the meta</p> <p>13 and the pooled analyses, were there any other ways in</p> <p>14 which those meta and pooled analyses were consistent, any</p> <p>15 other hallmarks of a consistency, other than the relative</p> <p>16 risk rates that you found notable?</p> <p>17 A I think if you could give some examples-- one--</p> <p>18 Q I am just asking you for your expert opinion.</p> <p>19 A One thing that is consistent is that for the two</p> <p>20 meta-analyses that are most recent, which is why I put</p> <p>21 most weight on them, they have all of the previous</p> <p>22 studies included, is that they included the same study,</p> <p>23 so that's similar between those two meta-analyses,</p> <p>24 Penninkilampi and Berge.</p> <p>25 The pooled analysis was a subset of those</p>	<p>1 Q (By Mr. Williams) Do you recognize Exhibit No. 15,</p> <p>2 Penninkilampi 2018, as one of the two studies that you</p> <p>3 described as excellent and supportive of your opinions?</p> <p>4 A Yes.</p> <p>5 Q Do you know the source or sources of funding for this</p> <p>6 paper?</p> <p>7 A No, I don't.</p> <p>8 Q Do you personally know who the author is?</p> <p>9 A No, I don't.</p> <p>10 Q Do you know what, if any, conflicts of interest any of</p> <p>11 the authors may have?</p> <p>12 A I am just looking to see.</p> <p>13 They claim no conflicts of interest.</p> <p>14 Q Do you know whether some of the authors are serving as</p> <p>15 consultants to Plaintiffs' counsel in this litigation?</p> <p>16 A No, I don't.</p> <p>17 Q Do you have any criticisms of the Penninkilampi 2018</p> <p>18 meta-analysis?</p> <p>19 MS. PARFITT: Objection; form.</p> <p>20 THE WITNESS: I think the only issue</p> <p>21 that I see are based on all of the-- all of the</p> <p>22 meta-analyses had this issue that depends on what results</p> <p>23 were available from the source studies, so if there</p> <p>24 weren't many studies that could do-- that could look at</p> <p>25</p>

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<p>1 subgroups, for example, or if there weren't enough--</p> <p>2 wasn't enough information to do dose response-- but by</p> <p>3 doing a meta-analysis, you have the best chance of being</p> <p>4 able to look at these because in the individual study</p> <p>5 those variables are-- the numbers of people within</p> <p>6 particular subgroups is going to be too small to be able</p> <p>7 to do an analysis.</p> <p>8 Q (By Mr. Williams) Did you do an independent verification</p> <p>9 of the data that the Penninkilampi study reports in--</p> <p>10 strike that.</p> <p>11 Did you do an independent verification that the data</p> <p>12 that this study reports is indeed accurate?</p> <p>13 A Did I do a meta-analysis myself on statistics? I did</p> <p>14 not.</p> <p>15 Q No, just whether the data that is reported accurately</p> <p>16 reflects what was reported in the study's records.</p> <p>17 A So there was a supplementary data table for this, I</p> <p>18 assume.</p> <p>19 I am pretty sure I looked at that and then compared</p> <p>20 the relative risk that I abstracted onto my data table,</p> <p>21 and I believe they were similar, but I don't see</p> <p>22 supplementary data here.</p> <p>23 Q Take a look at Page 46 of the document in the lower</p> <p>24 left-hand corner, Page 46 of Exhibit No. 15.</p> <p>25 Do you see that the Penninkilampi study includes,</p>	<p>1 correctly that are implemented.</p> <p>2 What I'm most intrigued by, all the cohort studies I</p> <p>3 reviewed, all seven of them, come up with just about the</p> <p>4 same overall relative risk of ever-use of talcum powder</p> <p>5 products and risk of ovarian cancer. It is consistently</p> <p>6 1.25 to 1.3, and that tells me that this is a robust</p> <p>7 finding because you see it in so many of these studies.</p> <p>8 Q (By Mr. Williams) Would you expect the association for</p> <p>9 long-term perineal talc use, say more than ten years, to</p> <p>10 be greater than, the same, or less than the association</p> <p>11 for any talc use, which could include a single use?</p> <p>12 A I would say it depends on what the individual study had</p> <p>13 in terms of sample size within categories.</p> <p>14 It really depends on sample size, and it depends on</p> <p>15 what the data look like.</p> <p>16 It's a difficult question to answer.</p> <p>17 Q Take a look at Page 46, Figure No. 2 of the Penninkilampi</p> <p>18 study, Exhibit No. 15.</p> <p>19 Do you see the explanation of the tables in Figure</p> <p>20 No. 2?</p> <p>21 Do you see that Table A refers to odds ratios for</p> <p>22 any perineal talc use?</p> <p>23 A Yes.</p> <p>24 Q And the odds ratio for the combined data, the data for</p> <p>25 any talc use in Table A, is 1.31?</p>
Page 183	Page 185
<p>1 for each study, a purported odds ratio, a lower limit and</p> <p>2 an upper limit?</p> <p>3 A Yes.</p> <p>4 Q Did you go back to the individual studies to verify that</p> <p>5 the numbers were recorded accurately?</p> <p>6 A I didn't compare the lower and upper limit of the</p> <p>7 confidence interval.</p> <p>8 Q Would it be important to you, in determining that a study</p> <p>9 is excellent, that the authors accurately report the odds</p> <p>10 ratio and the confidence intervals?</p> <p>11 A I think that would be useful, but for a meta-analysis,</p> <p>12 the data that goes into it, to my knowledge, are the odds</p> <p>13 ratios and the sample size, so I am not sure what</p> <p>14 variable-- which particular study you're talking about is</p> <p>15 not reported correctly.</p> <p>16 Q I am asking you whether it's important, not just whether</p> <p>17 it's notable.</p> <p>18 Would it be important to you, in determining--</p> <p>19 concluding that a study is excellent, that the authors</p> <p>20 accurately report the odds ratios and the confidence</p> <p>21 intervals; that is, if they get it wrong, that's not the</p> <p>22 sign of an excellent study, right?</p> <p>23 MS. PARFITT: Objection; form.</p> <p>24 THE WITNESS: I think in many studies</p> <p>25 there may be occasional data that are transformed not</p>	<p>1 Do you see that?</p> <p>2 A Yes.</p> <p>3 Q Now look at Table B.</p> <p>4 Do you see that this table refers to long-term</p> <p>5 perineal talc use?</p> <p>6 A Yes.</p> <p>7 Q The odds ratio for that combined data, the data for</p> <p>8 long-term use, is 1.25.</p> <p>9 Do you see that?</p> <p>10 A Yes.</p> <p>11 Q So as between Penninkilampi's reported overall</p> <p>12 association for any talc use, on the one hand, and its</p> <p>13 reporting for long-term talc use on the other, which one</p> <p>14 reflects a higher risk rate or odds ratio?</p> <p>15 A I would say they're very similar, 1.31 and 1.25, because</p> <p>16 the confidence interval include both, so the confidence</p> <p>17 interval in the top, 1.24 to 1.39, also includes the</p> <p>18 bottom odds ratio of 1.25. That tells me they're very</p> <p>19 similar.</p> <p>20 Q Doctor, I am just asking you a simple question.</p> <p>21 I asked you which one reflects a higher risk rate.</p> <p>22 MS. PARFITT: Objection; form, asked</p> <p>23 and answered.</p> <p>24 THE WITNESS: I am answering as an</p> <p>25 epidemiologist.</p>

<p style="text-align: right;">Page 186</p> <p>1 We would see those answers as quite similar.</p> <p>2 Q (By Mr. Williams) So epidemiologists would say that 1.31</p> <p>3 and 1.25, with the confidence intervals there, are the</p> <p>4 same?</p> <p>5 A I wouldn't say they're the same.</p> <p>6 Q So which one--</p> <p>7 MS. PARFITT: Counsel, please let her</p> <p>8 finish.</p> <p>9 Thank you.</p> <p>10 THE WITNESS: We wouldn't say they're</p> <p>11 the same, but we would state they could be similar.</p> <p>12 1.31 is clearly larger than 1.25, but they could</p> <p>13 be-- because of those confidence intervals, they could be</p> <p>14 similar numbers.</p> <p>15 Q (By Mr. Williams) When you evaluated the Penninkilampi</p> <p>16 study, did you take note that the authors omitted certain</p> <p>17 cohort data?</p> <p>18 MS. PARFITT: Objection; form.</p> <p>19 THE WITNESS: I noted that they</p> <p>20 included one paper from each study, which is really</p> <p>21 important.</p> <p>22 If you include more than one paper from each study,</p> <p>23 then you're over-counting or counting cases or noncases a</p> <p>24 second time.</p> <p>25 It's really important to only have one cohort</p>	<p style="text-align: right;">Page 188</p> <p>1 misstates her testimony.</p> <p>2 THE WITNESS: I would say because of</p> <p>3 the variable used, it was reasonable that they picked the</p> <p>4 Gonzalez, the first one.</p> <p>5 If the data had been collected in an identical way,</p> <p>6 then the third one would have been incorporated.</p> <p>7 Q (By Mr. Williams) Did the study explain that that was</p> <p>8 the reason why they omitted the Gates 2010 study?</p> <p>9 A I can't remember.</p> <p>10 I think they had an appendix.</p> <p>11 They talk about an appendix here with their</p> <p>12 rationale.</p> <p>13 Q We can check it later, but as you sit here today, can you</p> <p>14 remember any reference to--</p> <p>15 A I can't recall--</p> <p>16 Q Let me finish the question, if I could.</p> <p>17 Doctor, can you remember any reference, as you sit</p> <p>18 here, to the notion that they noted, in Penninkilampi,</p> <p>19 that they were not using the data from Gates 2010?</p> <p>20 MS. PARFITT: If you need to consult</p> <p>21 the document, please do.</p> <p>22 MR. WILLIAMS: My question is not</p> <p>23 asking her to read it.</p> <p>24 Q (By Mr. Williams) My question is whether you remember</p> <p>25 it?</p>
<p style="text-align: right;">Page 187</p> <p>1 represented in each of these meta-analyses.</p> <p>2 Q (By Mr. Williams) But if there had been additional</p> <p>3 cohorts after the first cohort, wouldn't it make sense to</p> <p>4 use the last one rather than the first?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: I think you are talking</p> <p>7 about the Nurses' Health Study.</p> <p>8 Q (By Mr. Williams) I am.</p> <p>9 A Whether they included the first one or the third one,</p> <p>10 because the second one wouldn't do them any good. There</p> <p>11 are only 200 cases. We don't know how they picked those.</p> <p>12 The third one, as I mentioned earlier, the problem</p> <p>13 with the third one is it used a different comparison to--</p> <p>14 than the first one.</p> <p>15 They are not comparing no-use versus ever-use.</p> <p>16 They're comparing no-use plus less-than-once-a-week</p> <p>17 versus higher levels, so you want to compare, as much as</p> <p>18 possible, nonusers versus users, which is-- they are</p> <p>19 trying to look at any ovarian-- sorry, any perineal talc</p> <p>20 use in the Category A would be more accurate to use the</p> <p>21 first Nurses' Health Study.</p> <p>22 Q Should I take your last answer to mean that you believe</p> <p>23 it is a good thing that the Gates 2000 study was omitted</p> <p>24 from the Penninkilampi analysis?</p> <p>25 MS. PARFITT: Objection; form,</p>	<p style="text-align: right;">Page 189</p> <p>1 MS. PARFITT: Without reading the</p> <p>2 document, do you recall?</p> <p>3 THE WITNESS: I don't recall.</p> <p>4 Q (By Mr. Williams) Take a look at Figure No. 2, Table C</p> <p>5 of Page 46 of that study.</p> <p>6 Do you see that it describes the purported</p> <p>7 association for increased risk of serous ovarian cancers?</p> <p>8 A Yes.</p> <p>9 Q And that's reporting the original Berge study from 2010,</p> <p>10 right?</p> <p>11 A 2000? Berge 2000?</p> <p>12 Q Excuse me, not 2010. Pardon me.</p> <p>13 2000-- Berge 2000?</p> <p>14 A Yes.</p> <p>15 Q As you sit there, you don't know-- you don't recall any</p> <p>16 explanation for the omission of the Gates 2010 data,</p> <p>17 right?</p> <p>18 MS. PARFITT: Objection; form.</p> <p>19 MR. WILLIAMS: I'm sorry, did I get an</p> <p>20 answer to that one?</p> <p>21 MS. PARFITT: No. She-- I think she</p> <p>22 is reading the document.</p> <p>23 THE WITNESS: Sorry.</p> <p>24 MS. PARFITT: Take your time.</p> <p>25 MR. WILLIAMS: My question-- well,</p>

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<p>1 hold on.</p> <p>2 Counsel, that just eats up the time.</p> <p>3 Q (By Mr. Williams) I am asking-- Doctor--</p> <p>4 MS. PARFITT: Counsel, you asked--</p> <p>5 MR. WILLIAMS: Let me finish--</p> <p>6 MS. PARFITT: Let me finish.</p> <p>7 You asked her in the middle of a question-- she</p> <p>8 hasn't answered it.</p> <p>9 Your question is right there.</p> <p>10 She hadn't answered it.</p> <p>11 She is reading the document. That's reflected on</p> <p>12 the camera.</p> <p>13 Give her-- if you want an answer to the question,</p> <p>14 give her an opportunity--</p> <p>15 Q (By Mr. Williams) Here is the problem, Doctor--</p> <p>16 MR. WILLIAMS: Are you done, Counsel?</p> <p>17 MS. PARFITT: I am.</p> <p>18 Q (By Mr. Williams) Here is the problem, Doctor:</p> <p>19 If I ask a question that is separate and apart from</p> <p>20 the document in front of you, and you choose to just read</p> <p>21 the entire document, all of our time is lost, so when I</p> <p>22 specifically ask you what you remember as you sit there,</p> <p>23 I would ask you not to read the document because that's</p> <p>24 not part of the question.</p> <p>25 Is that okay with you?</p>	<p>1 considered improper-- improper methodology.</p> <p>2 Usually these meta-analyses, and I believe they had</p> <p>3 it too, usually they will have supplementary data that's</p> <p>4 available also that will give more of their methods and</p> <p>5 the search terms, and I don't see that in what you've</p> <p>6 provided here today.</p> <p>7 Q (By Mr. Williams) Let me ask you to look at the Berge</p> <p>8 study from 2017. We will mark that as Exhibit No. 16.</p> <p>9 (Exhibit No. 16 marked</p> <p>10 for identification.)</p> <p>11</p> <p>12 Q (By Mr. Williams) Do you recognize Exhibit No. 16, which</p> <p>13 is the Berge 2017 study, as the other of the two</p> <p>14 meta-analyses that you described as excellent?</p> <p>15 A Yes.</p> <p>16 Q Please turn to Page 9 of the study.</p> <p>17 I direct your attention to the left-hand column, the</p> <p>18 last paragraph before "Acknowledgments."</p> <p>19 Do you see that?</p> <p>20 A Yes.</p> <p>21 Q The Berge study says, "Several aspects of our results,</p> <p>22 including the heterogeneity of results between</p> <p>23 case-control and cohort studies and the lack of a dose</p> <p>24 response with duration and frequency of use, however, do</p> <p>25 not support a causal interpretation of the association."</p>
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<p>1 MS. PARFITT: Counsel, that's actually</p> <p>2 not okay as a question.</p> <p>3 If the question is asking if this is a memory</p> <p>4 contest-- when she has the document in front of her, why</p> <p>5 aren't you allowing her to refer to the document?</p> <p>6 It's not a memory contest.</p> <p>7 Q (By Mr. Williams) Here is my question, Doctor:</p> <p>8 As you sit here, do you remember, one way or the</p> <p>9 other, whether the Penninkilampi study explains why it</p> <p>10 omitted any reference to the data from the Gates 2010</p> <p>11 report--</p> <p>12 MS. PARFITT: And I'm going to again</p> <p>13 object.</p> <p>14 Counsel, if she needs to look-- are you suggesting</p> <p>15 she can't look at the document to refresh her</p> <p>16 recollection? Is that what you want the record to</p> <p>17 reflect.</p> <p>18 Q (By Mr. Williams) You may answer, Doctor.</p> <p>19 MS. PARFITT: Take your time, Doctor.</p> <p>20 THE WITNESS: Looking at the methods</p> <p>21 here, I don't see that they've mentioned here why they</p> <p>22 chose particular studies.</p> <p>23 I do know that it's standard for meta-analysis to</p> <p>24 only include one study from a cohort.</p> <p>25 If you included more than one, it would be</p>	<p>1 Do you see that conclusion?</p> <p>2 A Yes, I do.</p> <p>3 Q The author's conclusion that the reported association did</p> <p>4 not support a causal interpretation, is the opposite of</p> <p>5 the conclusion that you would come up with in this case,</p> <p>6 correct?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 THE WITNESS: That's correct.</p> <p>9 Q (By Mr. Williams) If you would, keep the Berge 2017</p> <p>10 paper out.</p> <p>11 I will also ask you to refer for a moment to your</p> <p>12 own report, which is Exhibit No. 2, and specifically Page</p> <p>13 75.</p> <p>14 There is a table, Table No. 3, of data that you</p> <p>15 compiled about the various meta-analyses.</p> <p>16 Do you see that table?</p> <p>17 A Yes.</p> <p>18 Q And Berge 2017 is the second one that is referenced?</p> <p>19 A Yes.</p> <p>20 Q The right-most column of your table is called, "Dose</p> <p>21 response," correct?</p> <p>22 A Yes.</p> <p>23 Q And I'm going to talk a little more about dose response</p> <p>24 later, but for now can we agree that under the "Dose</p> <p>25 response" column for Berge 2017, you wrote, "Yes," for</p>

<p style="text-align: right;">Page 194</p> <p>1 duration and frequency-- did you write that?</p> <p>2 A Yes.</p> <p>3 Q And then you wrote a colon, and you went on to reflect</p> <p>4 that each ten-year increase in genital talc use was</p> <p>5 associated with a 16 percent increase in relative risk,</p> <p>6 and each increase of one application per week was</p> <p>7 associated with a five percent increase in relative risk.</p> <p>8 Do we have that right?</p> <p>9 A Yes.</p> <p>10 Q Now, if you would, please, turn back to the Berge study.</p> <p>11 Can you just-- we couldn't find it. Maybe you can,</p> <p>12 and this one I do want you to look through it.</p> <p>13 Would you please point out where the figures we just</p> <p>14 discussed from your table are actually reflected in the</p> <p>15 study?</p> <p>16 I'm sure it's there. We just couldn't find it.</p> <p>17 A I am not finding it.</p> <p>18 MS. PARFITT: Counsel, I can make it</p> <p>19 quicker, so we can save on time.</p> <p>20 Do you want me to show her where it is or have her</p> <p>21 keep looking?</p> <p>22 MR. WILLIAMS: I actually prefer that</p> <p>23 that not be what we do.</p> <p>24 MS. PARFITT: All right. I am just</p> <p>25 trying to move time along.</p>	<p style="text-align: right;">Page 196</p> <p>1 MS. PARFITT: Counsel, there are.</p> <p>2 If I can help, there's two Berge papers. One talks</p> <p>3 about the dose response and one does not, and I think you</p> <p>4 handed her the copy about-- that does not address the</p> <p>5 dose response, and the one she has in her binder</p> <p>6 addresses the dose response, both 2018 and very</p> <p>7 confusing, but--</p> <p>8 MR. WILLIAMS: So they are two</p> <p>9 different studies entirely?</p> <p>10 MS. PARFITT: No, they are actually</p> <p>11 very, very close, but one addressed the dose response and</p> <p>12 one did not.</p> <p>13 One, Doctor-- just for clarify, the one that</p> <p>14 Mr. McTiernan has in her notebook and that you all have</p> <p>15 in your reference material is Exhibit No.-- Reference</p> <p>16 No.-- what is that?</p> <p>17 THE WITNESS: 35.</p> <p>18 MS. PARFITT: 35 in the notebook,</p> <p>19 which is the Berge study that deals with the dose</p> <p>20 response.</p> <p>21 The one you handed her is the Berge that does not</p> <p>22 address the dose response or indicated there was no</p> <p>23 trend.</p> <p>24 MR. WILLIAMS: Let's mark for the</p> <p>25 record the one that Dr. McTiernan has in her hand as</p>
<p style="text-align: right;">Page 195</p> <p>1 Q (By Mr. Williams) If you could turn to Page 6 of the</p> <p>2 Berge meta-analysis, in the left-hand side, Table No. 3</p> <p>3 there, it says there-- it has a table in Table No. 3 that</p> <p>4 lists the duration of frequency, "Ever use of genital</p> <p>5 talc - results of meta-analysis."</p> <p>6 Do you see that?</p> <p>7 A Yes, Table No. 3?</p> <p>8 Q Right.</p> <p>9 It says, "Duration, ten years," and then there's a</p> <p>10 risk ratio of 0.97, with a confidence interval that drops</p> <p>11 below 1.0.</p> <p>12 Do you see that?</p> <p>13 A It looks like you have a different version than I have.</p> <p>14 Q Do I?</p> <p>15 A Yeah.</p> <p>16 Yours is-- my table looks different.</p> <p>17 That's odd.</p> <p>18 Q Are you looking at the-- I see, you are comparing-- just</p> <p>19 for the record, you are comparing what we gave you as</p> <p>20 Exhibit No. 16 with something in a notebook.</p> <p>21 Which notebook are you looking in?</p> <p>22 A My data-- all the references that I used.</p> <p>23 Q Okay.</p> <p>24 A I am just wondering--</p> <p>25 Q Are there different versions of it?</p>	<p style="text-align: right;">Page 197</p> <p>1 Exhibit No. 16A.</p> <p>2 MS. PARFITT: Very good.</p> <p>3 (Exhibit No. 16A marked</p> <p>4 for identification.)</p> <p>5</p> <p>6 MR. WILLIAMS: Do you happen to have</p> <p>7 another copy of that one?</p> <p>8 MS. PARFITT: Yeah, I can check.</p> <p>9 MR. WILLIAMS: Thank you.</p> <p>10 Q (By Mr. Williams) If you could look at Exhibit No. 16,</p> <p>11 and turn to Page 7.</p> <p>12 A So we are back to the other one?</p> <p>13 Q The original--</p> <p>14 A That I did not reference?</p> <p>15 Q Exhibit No. 16.</p> <p>16 Do you have that in front of you?</p> <p>17 A Page 7?</p> <p>18 Q Page 7, the right-hand column.</p> <p>19 Do you see in the right-hand column it says, "The</p> <p>20 presence or absence of a dose response is an important</p> <p>21 aspect to consider in assessing the plausibility of the</p> <p>22 causal nature of an association observed in a</p> <p>23 meta-analysis"?</p> <p>24 Did I read that right?</p> <p>25 A Yes, and the other version says the same thing.</p>



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<p>1 Q Okay. It goes on to say, I believe in both versions,</p> <p>2 "Although the numbers of studies included in the analysis</p> <p>3 of duration and frequency of genital talc use was not</p> <p>4 very large, and the exclusion of the reference category</p> <p>5 from the dose response analysis might have reduced the</p> <p>6 power of this analysis, the lack of a dose response --</p> <p>7 irrespective on an analytical approach chosen to combine</p> <p>8 categorical results across studies -- is a potentially</p> <p>9 important and novel contribution of this meta-analysis."</p> <p>10 Did I read that right?</p> <p>11 A Except the next version does not say, "lack of"-- if you</p> <p>12 read the paragraph from 16A, it does not say "lack of</p> <p>13 dose response."</p> <p>14 You have that right there.</p> <p>15 They have taken out that.</p> <p>16 They must have replaced this table with a corrected</p> <p>17 table, because that does show dose response in Table</p> <p>18 No. 3.</p> <p>19 Q So Table No. 3 in the two different versions of the Berge</p> <p>20 study are different?</p> <p>21 A Yes.</p> <p>22 That's why I was so confused.</p> <p>23 My data and my table was identical-- I abstracted</p> <p>24 this.</p> <p>25 MS. PARFITT: "This" being 16A?</p>	<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: And I tend to look at</p> <p>3 data, not necessarily what somebody has written as their</p> <p>4 conclusion.</p> <p>5 The data to me show that there is an increased risk</p> <p>6 of ovarian cancer with use of talcum powder products, and</p> <p>7 I think their data show it very clearly, and they have</p> <p>8 shown dose response relationships as well.</p> <p>9 Q (By Mr. Williams) My question to you is a little bit</p> <p>10 different.</p> <p>11 My question is:</p> <p>12 You disagree-- strike that.</p> <p>13 You disagree with the conclusion reached by the</p> <p>14 authors of the Berge study in that last sentence of their</p> <p>15 report that finds heterogeneity between the results of</p> <p>16 case-control and cohort studies, correct?</p> <p>17 MS. PARFITT: Objection; form,</p> <p>18 misstates her testimony.</p> <p>19 THE WITNESS: So you are only asking</p> <p>20 about the first part of that sentence not the causal</p> <p>21 interpretation, but the first part; is that correct?</p> <p>22 Q (By Mr. Williams) I am asking about the entirety of the</p> <p>23 sentence.</p> <p>24 A The entirety of the sentence?</p> <p>25 So yes, there was heterogeneity between the</p>
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<p>1 THE WITNESS: 16A, the version I used,</p> <p>2 and that's the version that was on the website and my</p> <p>3 library.</p> <p>4 Q (By Mr. Williams) Did you at any time read this study</p> <p>5 that was marked as Exhibit No. 16?</p> <p>6 A No.</p> <p>7 Q And how did you access the version at 16A?</p> <p>8 A This one I would have gotten from my Fred Hutch library.</p> <p>9 Q Let me have you look at Exhibit No. 16A.</p> <p>10 Do you have Page 9 in front of you?</p> <p>11 Can you turn to that page, just before the</p> <p>12 acknowledgments?</p> <p>13 A Okay.</p> <p>14 Q And this is the conclusion paragraph.</p> <p>15 Do you see that it begins, "In conclusion"?</p> <p>16 A Yes.</p> <p>17 Q In the 16A version that you have in front of you they</p> <p>18 wrote, "Several aspects of our results, including the</p> <p>19 heterogeneity of results between case-control and cohort</p> <p>20 studies, however, do not support a causal interpretation</p> <p>21 of the association."</p> <p>22 Do you see that?</p> <p>23 A Yes.</p> <p>24 Q And that was the conclusion of the Berge study from 2017</p> <p>25 in both versions 16 and 16A, correct?</p>	<p>1 case-control and cohort studies, but no, I do not think</p> <p>2 that that detracts from the causal association.</p> <p>3 Q What was the heterogeneity and the results between the</p> <p>4 case-control and the cohort studies that you observed?</p> <p>5 A There was a smaller increase in risk with the</p> <p>6 case-control studies.</p> <p>7 Q How much smaller?</p> <p>8 A Quite a bit.</p> <p>9 The relative risk was 1.02 in the cohort studies,</p> <p>10 1.26 in the case-control studies.</p> <p>11 Q And you conclude, based upon your own analysis, totally</p> <p>12 separate from the Berge study-- you conclude, based on</p> <p>13 your own analysis, that that disparity, 1.02 for the</p> <p>14 cohorts, 1.26 for the case-control studies, constitutes</p> <p>15 heterogeneity between those two types of studies?</p> <p>16 MS. PARFITT: Objection; misstates her</p> <p>17 testimony.</p> <p>18 She says she relied on the data.</p> <p>19 MR. WILLIAMS: Counsel, I would ask</p> <p>20 you not to coach.</p> <p>21 MS. PARFITT: I am not coaching.</p> <p>22 Let the record reflect I am not coaching. I am</p> <p>23 making it clear.</p> <p>24 THE WITNESS: I agreed that there's</p> <p>25 heterogeneity between those two sets of results, but that</p>

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<p>1 it does not subtract from the causal interpretation.</p> <p>2 The other thing I note when I look at a figure like</p> <p>3 this, Figure No. 2 in that Berge paper, that almost all</p> <p>4 of the relative risks are to the right of the line; "the</p> <p>5 line" being the line where the relative risk would be one</p> <p>6 or no effect.</p> <p>7 It's unusual to see so many studies with the</p> <p>8 relative risk over on the right side.</p> <p>9 I review a lot of meta-analyses, so this is unusual</p> <p>10 to see that level of consistency.</p> <p>11 Q (By Mr. Williams) So just so we're clear, you disagree</p> <p>12 with the second half, the second clause of the final</p> <p>13 sentence in the Berge study, but you agree with the first</p> <p>14 portion, correct?</p> <p>15 MS. PARFITT: Objection; form,</p> <p>16 misstates her testimony.</p> <p>17 THE WITNESS: I agree that the cohort</p> <p>18 studies have lower relative risks than do the</p> <p>19 case-control studies, yes.</p> <p>20 Q (By Mr. Williams) And you agree that that makes them</p> <p>21 heterogeneous, correct?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 Q (By Mr. Williams) Those two different types of studies?</p> <p>24 MS. PARFITT: Objection; form.</p> <p>25 THE WITNESS: That's part of the</p>	<p>1 A Ms. Parfitt sent them.</p> <p>2 Q Did she--</p> <p>3 A I am trying to remember if there was a website as well.</p> <p>4 Q Do you know how she obtained them?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: I do not know.</p> <p>7 Q (By Mr. Williams) Are you relying on the Taher 2018</p> <p>8 study for your opinion in this litigation?</p> <p>9 A I am not relying on the study, but it did add to my-- it</p> <p>10 does substantiate my opinion.</p> <p>11 It's very similar results to what we saw in the</p> <p>12 other meta-analyses.</p> <p>13 Q Is the Taher 2018 article peer-reviewed?</p> <p>14 A Not to my knowledge, but I don't know what process it</p> <p>15 went through to get to this point.</p> <p>16 Q Do you know one way or the other whether it has been</p> <p>17 accepted for publication?</p> <p>18 A I don't know.</p> <p>19 Q Do you know the source or sources of funding for the</p> <p>20 Taher 2018 article?</p> <p>21 A I think it said Health Canada, but--</p> <p>22 Q Other than the reference to Health Canada-- it references</p> <p>23 a contract with Health Canada.</p> <p>24 Other than that, do you have any knowledge as to the</p> <p>25 sources of funding?</p>
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<p>1 definition of "heterogeneity," is to see differences.</p> <p>2 Q (By Mr. Williams) Let me ask you some questions about</p> <p>3 the Taher 2018 study.</p> <p>4 We will mark that study as Exhibit No. 17.</p> <p>5 (Exhibit No. 17 marked</p> <p>6 for identification.)</p> <p>7</p> <p>8 Q (By Mr. Williams) The Taher 2018 study is not one of the</p> <p>9 articles that you originally included in your reference</p> <p>10 list, right?</p> <p>11 A That's correct.</p> <p>12 It was made public after my report was submitted.</p> <p>13 Q It is included in the additional materials to Dr. Anne</p> <p>14 McTiernan, a listing that we marked earlier today?</p> <p>15 A Yes.</p> <p>16 Q Have you read the entire transcript?</p> <p>17 A Yes, I have.</p> <p>18 Q Did you have access to this article before it was</p> <p>19 published?</p> <p>20 A It's not published. It's a draft manuscript.</p> <p>21 Q Do you have access to the appendixes or supplemental</p> <p>22 tables that are referenced in the publication?</p> <p>23 A Yes.</p> <p>24 I don't have them with me, but I did have access.</p> <p>25 Q How did you have access to them?</p>	<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: All I know is source of</p> <p>3 funding is Health Canada, what it says in the paper.</p> <p>4 Q (By Mr. Williams) Do you personally know any of the</p> <p>5 authors who are listed on the first page?</p> <p>6 A No, I don't.</p> <p>7 Q Have you discussed your opinion on talc and ovarian</p> <p>8 cancer with any of those authors?</p> <p>9 A No, I haven't.</p> <p>10 Q Do you know what conflicts of interest, if any, the</p> <p>11 authors may have?</p> <p>12 MS. PARFITT: Objection; form.</p> <p>13 THE WITNESS: No, I don't.</p> <p>14 Q (By Mr. Williams) Do you know whether some of the</p> <p>15 authors are serving as consultants to the plaintiffs in</p> <p>16 this litigation?</p> <p>17 A No, I don't.</p> <p>18 Q Were you asked to be a co-author of that paper?</p> <p>19 A No, I wasn't.</p> <p>20 Q Did you provide comments to it?</p> <p>21 A No, I didn't.</p> <p>22 Q Did the authors ever consult you in any way in connection</p> <p>23 with their publication?</p> <p>24 A No, they didn't.</p> <p>25 Q Did you attend the National Cancer Institute directors'</p>

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<p>1 meeting in Lyon, France on July 11, 2013 of last year,</p> <p>2 2018?</p> <p>3 A No, I didn't.</p> <p>4 Q The Taher study contains a meta-analysis, right?</p> <p>5 A That's correct.</p> <p>6 Q If you turn to Page 28, Page 28 calculates or reports an</p> <p>7 overall relative risk of 1.28 with a confidence interval</p> <p>8 of 1.20 to 1.37, right?</p> <p>9 A It's written there-- okay, yes.</p> <p>10 Q If you turn to Page 49, under the heading, "Conclusion,"</p> <p>11 the very last sentence says, in part, "The present</p> <p>12 comprehensive evaluation of all currently available</p> <p>13 relevant data indicates that perineal exposure to talc</p> <p>14 powder is a possible cause of ovarian cancer in humans,"</p> <p>15 right?</p> <p>16 A Yes, I see that.</p> <p>17 Q Do you agree that the 2018 paper represents a</p> <p>18 comprehensive evaluation of all currently available</p> <p>19 relative data?</p> <p>20 A It appeared to be a relevant meta-analysis.</p> <p>21 As you mentioned, it's not peer-reviewed.</p> <p>22 I would like to see it be peer-reviewed, but it has</p> <p>23 a remarkably similar relative risk of the other</p> <p>24 meta-analyses that I've reviewed that were peer-reviewed,</p> <p>25 so not only the most recent comprehensive ones but also</p>	<p>1 International Association for Research of Cancer, 2010</p> <p>2 monograph with respect to perineal use of talc, right?</p> <p>3 MS. PARFITT: Objection; form.</p> <p>4 THE WITNESS: 2010 monograph was from</p> <p>5 data up until 2007, so they did not have the benefit of</p> <p>6 the last ten years.</p> <p>7 I believe IARC would have given a stronger</p> <p>8 characterization of talcum powder applied to the perineum</p> <p>9 if they were to review the data today, but they did</p> <p>10 categorize talcum applied to the perineum as a possible</p> <p>11 carcinogen Grade 2B.</p> <p>12 Q (By Mr. Williams) I would move to strike that as</p> <p>13 nonresponsive, Doctor, but my question is:</p> <p>14 You are speculating when you say what IARC would or</p> <p>15 would not have done; are you not?</p> <p>16 MS. PARFITT: Objection--</p> <p>17 THE WITNESS: Correct.</p> <p>18 Q (By Mr. Williams) In fact, and point of fact, in 2010</p> <p>19 IARC, in the 2010 monograph, reached a conclusion that</p> <p>20 perineal exposure to talcum powder is a possible cause of</p> <p>21 ovarian cancer, and they put it in Group 2B, right?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 THE WITNESS: Using data that they had</p> <p>24 available and through 2007, then yes, they classified it</p> <p>25 that way in 2B.</p>
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<p>1 the previous meta-analyses.</p> <p>2 Q Do you agree with the conclusion of the authors in Taher</p> <p>3 2018 that perineal exposure to talcum powder is a</p> <p>4 possible cause of ovarian cancer in humans?</p> <p>5 A I believe that it is a cause of ovarian cancer in humans.</p> <p>6 Q My question is different.</p> <p>7 My question is whether you agree with the conclusion</p> <p>8 of the authors, what they wrote here, which is that</p> <p>9 perineal exposure to talcum powder is a possible cause of</p> <p>10 ovarian cancer in humans.</p> <p>11 A And I am saying I would use a stronger statement than</p> <p>12 that.</p> <p>13 I would say these data support a causal association</p> <p>14 with cancer, ovarian cancer.</p> <p>15 Q So you disagree with them?</p> <p>16 A Yes.</p> <p>17 Q It would be faster if you just do that upfront.</p> <p>18 A I like to be exact. Sorry.</p> <p>19 Q Just so we're clear, you disagree with the conclusion of</p> <p>20 the authors in the Taher study, that talcum powder is a</p> <p>21 possible cause of ovarian cancer in humans, right?</p> <p>22 A I believe that talcum powder product use is the cause of</p> <p>23 ovarian cancer in humans, based on my review.</p> <p>24 Q The conclusion in this Taher 2018 article is the same as</p> <p>25 that-- as the conclusion that was reached in the IARC,</p>	<p>1 Q (By Mr. Williams) Do you have any criticisms of the</p> <p>2 Taher 2018 meta-analysis?</p> <p>3 A As I mentioned before, it has remarkable similar results</p> <p>4 to the other meta-analyses, so that gave me some</p> <p>5 confidence.</p> <p>6 I was a little curious why they picked-- I think</p> <p>7 it's some of the supplementary tables.</p> <p>8 They picked relative risk for some of the-- a couple</p> <p>9 of the studies that I would not have picked, and some of</p> <p>10 the meta-analyses did not pick-- when many of the studies</p> <p>11 have presented data, it's a little difficult to tell</p> <p>12 which of the data are the most basic, meaning no use of</p> <p>13 talcum powder products to the perineum versus any use,</p> <p>14 and sometimes it's difficult to determine which is the</p> <p>15 correct relative risk to pick, odds ratio, but I don't</p> <p>16 have that here, don't have the supplemental data here.</p> <p>17 Q Other than what you've just expressed, do you have any</p> <p>18 other criticisms?</p> <p>19 A I didn't see other concerns.</p> <p>20 I think Table No. 2, the summary for the Bradford</p> <p>21 Hill criteria of causation, they--</p> <p>22 Q Could you give me the page?</p> <p>23 A I'm sorry, Page 25, Table No. 2.</p> <p>24 Q Thank you.</p> <p>25 A The question I had there is when they looked at strengths</p>

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<p>1 of association, they looked across individual studies and</p> <p>2 didn't take into account the meta-analyses, so I think</p> <p>3 they could have used their own data as well as the other</p> <p>4 meta-analyses, and they could have mentioned that there</p> <p>5 as part of strengths of association.</p> <p>6 Q Have you now listed all of your criticisms of the study?</p> <p>7 A Yes, I believe so.</p> <p>8 Q Do you believe it was improper of the authors of this</p> <p>9 study to include both the Wu 2009 and the Wu 2015 studies</p> <p>10 in the meta-analysis, as reflected on Page 29?</p> <p>11 A I would have to look back and see if those are the same--</p> <p>12 if they include some of the same cases.</p> <p>13 Q If they included the same cases, then for the reasons you</p> <p>14 described earlier today, you would criticize this study</p> <p>15 because there would be double counting, right?</p> <p>16 MS. PARFITT: Objection.</p> <p>17 THE WITNESS: Yes.</p> <p>18 Q (By Mr. Williams) Please turn to Page 3 on-- Figure</p> <p>19 No. 3 on Page 39.</p> <p>20 It says, underneath that table, "Figure No. 3:</p> <p>21 Ovarian cancer risk estimates at increasing levels of</p> <p>22 exposure to talc, as reported from multiple studies."</p> <p>23 Do you see that?</p> <p>24 A Yes.</p> <p>25 Q Does Figure No. 3 provide evidence of a dose-response</p>	<p>1 THE WITNESS: That's what they stated,</p> <p>2 yes.</p> <p>3 Q (By Mr. Williams) And the importance of statistical</p> <p>4 significance is-- strike that.</p> <p>5 Statistical significance is evaluated in order for</p> <p>6 epidemiologists and other researchers to try to rule out</p> <p>7 chance, right?</p> <p>8 A Statistical significance depends largely on sample size,</p> <p>9 and it's merely a probability, so if you have a P value</p> <p>10 of 0.05, it means you have a five percent chance of</p> <p>11 making an error.</p> <p>12 There's nothing magical about 0.05.</p> <p>13 0.06 could be a very relevant study as well.</p> <p>14 Statistical significance is often determined-- it's</p> <p>15 often thought to be statistically significant if the P</p> <p>16 value is less than or equal to 0.05.</p> <p>17 As I said, it's not magical.</p> <p>18 It really depends on sample size, so when I look at</p> <p>19 studies, I look at the totality of evidence, I look at</p> <p>20 consistency, and I look at whether the relative risk is</p> <p>21 above one consistently.</p> <p>22 Q What I'm trying to get at, Doctor, is whether-- is the</p> <p>23 purpose of statistical significance.</p> <p>24 Will you agree with me, and you can say "no," you</p> <p>25 can say "yes," you can say "maybe," but do you agree with</p>
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<p>1 relationship, in your opinion?</p> <p>2 A I don't think I could evaluate that because I don't see</p> <p>3 an explanation of where they get that data from.</p> <p>4 Q Let me ask you to look back on-- at Page 29-- actually,</p> <p>5 Page 25. Excuse me.</p> <p>6 Do you see where it says, "Consistency: 15 out of</p> <p>7 30 studies reported positive and significant associations</p> <p>8 reported in:" and then there's a colon and four bullet</p> <p>9 points?</p> <p>10 Do you see that?</p> <p>11 A Yes.</p> <p>12 Q 15 out of 30 is 50 percent of the case-control studies,</p> <p>13 right-- 15 out of 30 is 50 percent of the total number of</p> <p>14 studies reported, right?</p> <p>15 MS. PARFITT: Objection; form.</p> <p>16 THE WITNESS: Yes, that would be 50</p> <p>17 percent.</p> <p>18 Q (By Mr. Williams) And 50 percent of the studies did not</p> <p>19 find a positive significant association that was</p> <p>20 statistically significant, correct?</p> <p>21 MS. PARFITT: Objection; form,</p> <p>22 misstates the data.</p> <p>23 THE WITNESS: You are asking me if</p> <p>24 that's what it stated?</p> <p>25 MR. WILLIAMS: Yes.</p>	<p>1 me or not that the purpose of evaluating statistical</p> <p>2 significance is to try to rule out the possibility that</p> <p>3 results are a result of chance?</p> <p>4 A I would modify that.</p> <p>5 I would say you would look at a statistical test in</p> <p>6 order to determine what is the likelihood that chance</p> <p>7 explained your result.</p> <p>8 I wouldn't say the word "rule out," because, as I</p> <p>9 mentioned, a P value of 0.06 could be as relevant as a P</p> <p>10 value of 0.05.</p> <p>11 It really depends on the sample size.</p> <p>12 Q You are familiar with IARC ratings?</p> <p>13 You mentioned them earlier today, right?</p> <p>14 A Yes.</p> <p>15 Q And you know that IARC ratings for Group 2B, which is</p> <p>16 what IARC found for talc in 2006, I think, was that talc</p> <p>17 should be listed as a possible cause of ovarian cancer,</p> <p>18 correct?</p> <p>19 MS. PARFITT: Objection; misstates the</p> <p>20 document.</p> <p>21 THE WITNESS: Maybe I should reframe</p> <p>22 my answer.</p> <p>23 My understanding is a classification 2B means a</p> <p>24 possible carcinogen.</p> <p>25 Q (By Mr. Williams) Okay. And as you sit there, can you</p>

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<p>1 tell us what the definition of a Group 2B substance is,</p> <p>2 according to IARC?</p> <p>3 A I don't have that memorized.</p> <p>4 I do know that there are different panels set up for</p> <p>5 each carcinogen, and there is an overall group that helps</p> <p>6 the scientists to decide what classification to put</p> <p>7 something in, but that-- it's not a clear-cut,</p> <p>8 necessarily.</p> <p>9 The scientific panel has to look at the totality of</p> <p>10 evidence as they decide what level of evidence they have.</p> <p>11 Q Does it sound familiar to you that in assigning a Group</p> <p>12 2B status for talcum powder, that the IARC team concluded</p> <p>13 that chance, bias, and confounding factors could not be</p> <p>14 ruled out?</p> <p>15 A I don't have the document in front of me.</p> <p>16 I would need to look at that.</p> <p>17 Do we have it?</p> <p>18 Q We do, and I will get to it in a minute.</p> <p>19 I am asking you, as you sit here, do you have any</p> <p>20 memory that the way that IARC analyzes whether a</p> <p>21 substance is in Group 2B or some other grouping, is that</p> <p>22 if chance, bias, and confounding factors cannot be ruled</p> <p>23 out, then the substance should be in Group 2B?</p> <p>24 MS. PARFITT: Objection; form.</p> <p>25 Again, object to the memory aspect of this.</p>	<p>1 Q There you refer to sample size as opposed to the number</p> <p>2 of cases, did you not, in that sentence that I just read</p> <p>3 you?</p> <p>4 A The reason I'm hesitating is I do two sample size</p> <p>5 calculations.</p> <p>6 In here I am talking about calculation-- I was</p> <p>7 talking about the sample sizes from case-control studies,</p> <p>8 and after this link that I provide, the calculation</p> <p>9 showed the minimum number of cases in controls need to be</p> <p>10 931 each, and then there's another place where I</p> <p>11 calculate the cohort sizes.</p> <p>12 Q Can we stay here for just one moment on Page 48?</p> <p>13 A Yes.</p> <p>14 Q First of all, you performed what is known as a power</p> <p>15 calculation to determine the sample size that you</p> <p>16 believed is required for a study?</p> <p>17 A That's correct.</p> <p>18 Q And you place particular importance, you told me a moment</p> <p>19 ago, on the number of cancer cases total, correct?</p> <p>20 A That's correct.</p> <p>21 Q Based on your calculation, you concluded that the minimum</p> <p>22 number of cases would need to be 931, correct?</p> <p>23 A That's correct, to have-- to have good power to detect</p> <p>24 relative risk of 1.3 with statistical significance of</p> <p>25 0.05.</p>
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<p>1 If there's a document available, you should show it</p> <p>2 to her.</p> <p>3 THE WITNESS: And I can't remember.</p> <p>4 Q (By Mr. Williams) One reason that you have stated for</p> <p>5 the lack of statistical significance in cohort studies is</p> <p>6 the sample size in those studies, correct?</p> <p>7 A The number of cases, the sample size of cases, yes.</p> <p>8 Q Right.</p> <p>9 So now in your last answer, you are distinguishing</p> <p>10 between the total sample size on the one hand and the</p> <p>11 number of cases of cancer on the other, correct?</p> <p>12 A Yes.</p> <p>13 Q What's important for your analysis, in terms of sample</p> <p>14 size, is the number of cancer cases?</p> <p>15 A That's correct.</p> <p>16 Q You believe that the number of cases affects the</p> <p>17 statistical power of the studies?</p> <p>18 A Yes.</p> <p>19 Q Doctor, let me ask you about your report though.</p> <p>20 If you could look at Exhibit No. 2, Page 48, do you</p> <p>21 see there in the middle of the page it says, "I interpret</p> <p>22 the lack of statistical significance in some source</p> <p>23 studies as being due to the small sample sizes of many of</p> <p>24 these studies"?</p> <p>25 A Yes.</p>	<p>1 Q You also concluded that the minimum number of controls</p> <p>2 would need to be 931, correct?</p> <p>3 A That's the simplest model.</p> <p>4 Different case-control studies will have different</p> <p>5 numbers, and that can affect the power one way or the</p> <p>6 other.</p> <p>7 I just did a simple calculation, but you could have</p> <p>8 power increased by having a small number more of controls</p> <p>9 or a small number of more cases, so it depends on how--</p> <p>10 how it ends up working out, but this is the simplest</p> <p>11 model.</p> <p>12 Q The point you were making in performing your power</p> <p>13 calculation was that meta-analyses, with their larger</p> <p>14 combined sample sizes, can be used to overcome that lack</p> <p>15 of statistical power; is that true?</p> <p>16 A Yes.</p> <p>17 Q One of the two meta-analyses that you called excellent</p> <p>18 combine data from three of the cohort studies to arrive</p> <p>19 at a single risk estimate.</p> <p>20 Do you remember that?</p> <p>21 A No, I don't.</p> <p>22 Which study?</p> <p>23 Q Let me ask you to look at the 2017 Berge analysis, and</p> <p>24 let's use Exhibit No. 16A.</p> <p>25 MS. PARFITT: Not cutting you off</p>



<p style="text-align: right;">Page 218</p> <p>1 right now, but maybe when you get to a good place, we can 2 take a break.</p> <p>3 MR. WILLIAMS: Okay. Sure.</p> <p>4 Q (By Mr. Williams) Do you have Exhibit No. 16A in front 5 of you?</p> <p>6 A I do.</p> <p>7 Q And I would like to have you focus on Page-- I believe 8 it's 7, Figure No. 2.</p> <p>9 Do you see where the authors list the three cohort 10 studies they analyzed?</p> <p>11 A Yes.</p> <p>12 Q Gates 2010, Houghton 2014, Gonzalez 2016?</p> <p>13 A Hold on a minute.</p> <p>14 Q And "Houghton" is--</p> <p>15 A Sorry.</p> <p>16 (Phone interruption) I was getting a call on this. 17 I am going to turn it off.</p> <p>18 Q Do you see in the middle of Page 7 the reference to 19 Gates, Houghton, and Gonzalez?</p> <p>20 Do you see the reference in Figure No. 2, middle of 21 the page, that says, "Cohort studies," and it references 22 those three studies?</p> <p>23 A Yes.</p> <p>24 Q And "Houghton," for the record, is H-O-U-G-H-T-O-N. 25 Now, look back one page to Page 6 of Exhibit</p>	<p style="text-align: right;">Page 220</p> <p>1 Q If you add those two numbers together, what do you get?</p> <p>2 A I don't know exactly-- over 1300.</p> <p>3 Q 1300 is more than 931, correct?</p> <p>4 A Yes.</p> <p>5 Q 900 and 1300-- to be precise, it's 1372. You add those 6 two numbers together.</p> <p>7 1372 cancer cases is well above the 931 that you 8 calculated would be necessary to find statistical 9 significance, right?</p> <p>10 A Yes.</p> <p>11 Q And because of the nature of cohort studies, there were 12 also many times that the number of women who did not get 13 ovarian cancer-- right-- that's a separate number?</p> <p>14 A What did you say about the cohort studies?</p> <p>15 Q In addition to the cases where women ultimately, 16 unfortunately, were diagnosed with cancer, the 1372, 17 there are many times that number of women who were 18 followed along in their lives who did not get ovarian 19 cancer, correct?</p> <p>20 A Yes.</p> <p>21 Q So this meta-analysis is sufficient, under your power 22 calculation, to be able to find a statistically 23 significant association, true?</p> <p>24 A Yes, and that's why overall we see 1.22 is statistically 25 significant.</p>
<p style="text-align: right;">Page 219</p> <p>1 No. 16A, and take a look at the paragraph starting at the 2 top of the right column.</p> <p>3 Do you see that one?</p> <p>4 A Yes.</p> <p>5 Q About halfway down that paragraph the authors state as 6 follows, "It should be noted that the cohort studies 7 included in the meta-analysis comprised a total of 429 8 cases of ovarian cases exposed to genital talc and 943 9 unexposed cases: the statistical power of the 10 meta-analysis of these cohort studies to detect a risk 11 ratio of 1.25, similar to the result of the meta-analysis 12 of case-control studies, was 0.99. Thus, low power of 13 cohort studies cannot be invoked as explanation of the 14 heterogeneity of results."</p> <p>15 Did I read that correctly?</p> <p>16 A Yes, you did.</p> <p>17 Q Now, they reference here in the Berge study-- strike 18 that. Let me start over.</p> <p>19 The Berge study is one of the two meta-analyses that 20 you said is an excellent study, correct?</p> <p>21 A Yes.</p> <p>22 Q And what they list here on Page No. 6 is 429 cases of 23 ovarian cancer and 943 unexposed cases.</p> <p>24 Is that correct?</p> <p>25 A Yes.</p>	<p style="text-align: right;">Page 221</p> <p>1 Q Please explain.</p> <p>2 A Pardon?</p> <p>3 Q Please explain your answer.</p> <p>4 A The overall relative risk of 1.22, the confidence 5 interval is 1.13 to 1.3-- you see the overall 6 statistically significant effect.</p> <p>7 Q That wasn't what they concluded for the cohort studies 8 though, correct?</p> <p>9 The cohort studies had the following on page-- I am 10 looking at Page 7, Figure No. 2.</p> <p>11 The cohort studies, for Gates it was 1.12, for 12 Gonzalez it was 0.73-- excuse me, I misspoke.</p> <p>13 For Gates it was 1.06, for Houghton it was 1.12, and 14 for Gonzalez the relative risk was 0.73, correct?</p> <p>15 A 0.73, yes.</p> <p>16 Q So if you look at the cohort studies, separate and apart 17 from the case-control studies that are listed above, we 18 can agree that the relative risk is nowhere near 1.22?</p> <p>19 MS. PARFITT: Objection; form.</p> <p>20 Q (By Mr. Williams) Right?</p> <p>21 MS. PARFITT: Objection; form.</p> <p>22 THE WITNESS: Yeah, I think the-- the 23 way I look at the meta-analysis, is I look at all of the 24 studies together.</p> <p>25 I don't just look at one particular type separate</p>

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<p>1 from others, but as an example, the Houghton study, which</p> <p>2 had about 400 cases, I believe, the Women's Health</p> <p>3 Initiative, with a relative risk of 1.12, if they had had</p> <p>4 900 cases, that probably would have been a statistically</p> <p>5 significant result, so that's what the power calculation</p> <p>6 does.</p> <p>7 In this case you have the Gonzalez-- the sister</p> <p>8 study is what brings the relative risk down closer to one</p> <p>9 because you do have one negative result there, but</p> <p>10 overall, looking at all of the meta-analyses-- all of the</p> <p>11 studies together, you see definitely a trend towards a</p> <p>12 relative risk consistently above one.</p> <p>13 Q (By Mr. Williams) Now-- have you completed your answer?</p> <p>14 A Yes.</p> <p>15 Q You just mentioned a moment ago that with a relative risk</p> <p>16 of 1.12, if they had 900 cases, they probably would have</p> <p>17 been a statistically significant-- that probably would</p> <p>18 have been a statistically significant result.</p> <p>19 When you say that that probably would have been the</p> <p>20 case in the women's health study, you're speculating</p> <p>21 there, aren't you?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 THE WITNESS: I am speculating from my</p> <p>24 previous experience with working with the Women's Health</p> <p>25 Initiative, that with very large numbers of cases if you</p>	<p>1 that was available at the time, and in total that's what</p> <p>2 I look at.</p> <p>3 The issue with the cohort studies are that the</p> <p>4 information on talcum powder product use was collected at</p> <p>5 one point in time. It was never updated, and it was not</p> <p>6 retrospective, so we don't know what-- lifetime use in</p> <p>7 those cohort studies.</p> <p>8 Q (By Mr. Williams) We'll take a break in a moment, but my</p> <p>9 question before the break is this:</p> <p>10 I was asking, for purposes of my question, for you</p> <p>11 to exclude case-control studies from your analysis.</p> <p>12 My question was:</p> <p>13 If you were doing an analysis that had been based on</p> <p>14 the cohort studies, and not on your analysis of the</p> <p>15 case-control study relative risks, you would not have</p> <p>16 been able to conclude that perineal use of talc causes</p> <p>17 ovarian cancer with a 1.02 relative risk that is not</p> <p>18 statistically significant, right?</p> <p>19 MS. PARFITT: Objection; form,</p> <p>20 misstates her testimony and her opinions.</p> <p>21 THE WITNESS: I think that's</p> <p>22 speculative because I wouldn't have ignored the</p> <p>23 significant amount of data from case-control studies.</p> <p>24 Q (By Mr. Williams) On the question of whether or not the</p> <p>25 difference between case-control and cohort studies may be</p>
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<p>1 have-- even with small relative risk you will have a</p> <p>2 statistically significant result, an amount, that you</p> <p>3 would correct on speculating what would be seen with this</p> <p>4 particular data set.</p> <p>5 Q (By Mr. Williams) Let me ask you to focus on Page 7 of</p> <p>6 the exhibit and Figure No. 2, again, and the cohort</p> <p>7 studies for Exhibit No. 16A, the Berge study.</p> <p>8 You see there's a subtotal there for the cohort</p> <p>9 studies at the bottom of the table, right?</p> <p>10 A Yes.</p> <p>11 Q The combined relative risk for the cohort studies is</p> <p>12 1.02, no statistical significance, correct?</p> <p>13 A Correct.</p> <p>14 Q The confidence interval combined for those was 0.85 to</p> <p>15 1.20, correct?</p> <p>16 A Correct.</p> <p>17 Q If you had been basing your analysis on the cohort</p> <p>18 studies and not on an analysis of the case-control</p> <p>19 studies, you would not have been able to reach your</p> <p>20 conclusion that use of talc is a cause of ovarian cancer,</p> <p>21 true?</p> <p>22 MS. PARFITT: Objection; form,</p> <p>23 misstates the evidence.</p> <p>24 THE WITNESS: I looked at the totality</p> <p>25 of evidence and looked at all of the epidemiologic data</p>	<p>1 due to sample size and resulting low power, you come to</p> <p>2 the opposite conclusion as the authors of the Berge 2017</p> <p>3 study that you are relying upon, correct?</p> <p>4 MS. PARFITT: Objection; form,</p> <p>5 misstates her testimony.</p> <p>6 THE WITNESS: I am not sure why you</p> <p>7 come to that.</p> <p>8 I have the opposite conclusion.</p> <p>9 Q (By Mr. Williams) Well, the authors of the Berge study</p> <p>10 concluded that-- the authors of the Berge study concluded</p> <p>11 that low power of cohort studies cannot be invoked as an</p> <p>12 explanation of the heterogeneity of results, right?</p> <p>13 That's what they wrote?</p> <p>14 A That's what they wrote.</p> <p>15 Q On the question of whether or not the difference between</p> <p>16 case-control and cohort studies may be due to sample size</p> <p>17 and resulting low power, you come to the opposite</p> <p>18 conclusion as the authors of the Berge study, correct?</p> <p>19 MS. PARFITT: Objection; form.</p> <p>20 THE WITNESS: I don't remember coming</p> <p>21 to the opposite conclusion.</p> <p>22 I have opposite-- I have alternative reason why I</p> <p>23 think the cohort studies could have lower relative risk</p> <p>24 than the case-control studies, and-- which I've just</p> <p>25 stated about the way the exposures are collected.</p>

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<p>1 Q (By Mr. Williams) In your report, Dr. McTiernan, you</p> <p>2 dealt with the heterogeneity issue between the relative</p> <p>3 risk findings for case-controls versus the relative risk</p> <p>4 findings for cohorts.</p> <p>5 You dealt with that disparity by doing a power</p> <p>6 calculation and concluding that you needed 931 cases in</p> <p>7 order to have sufficient power.</p> <p>8 That's what you said, right?</p> <p>9 A A study-- I was talking about individual studies.</p> <p>10 I wasn't talking about the combined group of cohort</p> <p>11 studies.</p> <p>12 Q What the authors said on Page 6 of Exhibit No. 16A was,</p> <p>13 "Thus, low power of cohort studies cannot be invoked as</p> <p>14 an explanation of the heterogeneity of results."</p> <p>15 They said that, right?</p> <p>16 A Yes, and I think they mean the cohort studies combined.</p> <p>17 Q I'm sorry?</p> <p>18 A They're talking about the cohort studies combined.</p> <p>19 I'm talking about individual studies.</p> <p>20 Q And you disagree with that conclusion, true or not true?</p> <p>21 MS. PARFITT: Objection; form.</p> <p>22 THE WITNESS: I think that they're</p> <p>23 correct in what they're saying, that they had sufficient</p> <p>24 power to find a relative risk if it was there, if the</p> <p>25 study was done directly when they added those three</p>	<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: You are talking about</p> <p>3 this-- yes.</p> <p>4 Q (By Mr. Williams) In your last answer or two answers</p> <p>5 ago, you referenced the fact that two of the cohort</p> <p>6 studies had relative risks above one.</p> <p>7 Do you remember saying that?</p> <p>8 A Yes.</p> <p>9 Q You are referring to Gates, which was 1.06, and Houghton,</p> <p>10 which is 1.12, correct?</p> <p>11 A Correct.</p> <p>12 Q The other relative risk was 0.73, correct?</p> <p>13 A Correct.</p> <p>14 Q If it had been statistically significant, that would show</p> <p>15 a protective effect from the use of talc, correct?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 THE WITNESS: Correct.</p> <p>18 Q (By Mr. Williams) Do you think that relative risks of</p> <p>19 1.06 and 1.12 are weak? strong? moderate?</p> <p>20 How would you characterize those numbers?</p> <p>21 MS. PARFITT: Objection; form.</p> <p>22 THE WITNESS: I tend to look at the</p> <p>23 number of what they are, rather than giving an adjective</p> <p>24 to it.</p> <p>25 I believe one possibility for these cohort studies</p>
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<p>1 studies together, but I'm saying there were alternative</p> <p>2 reasons why the relative risk is lower, so there's two</p> <p>3 issues, the relative risk and the power and statistical</p> <p>4 significance, and the relative risk for two of those</p> <p>5 studies is over one.</p> <p>6 They used Gates-- Gertig had a little bit different</p> <p>7 level, but the data was collected in very different ways</p> <p>8 for cohort studies than case-control studies.</p> <p>9 Another problem with the cohort studies is that they</p> <p>10 did not follow the women for very long, on average, which</p> <p>11 was the case of 12 studies that have lifetime exposure,</p> <p>12 so the cohort studies may have not had all of the cases</p> <p>13 develop that were going to be developed, so there are</p> <p>14 reasons-- but it's two different reasons: the effect</p> <p>15 size, which is the relative risk, and the statistical</p> <p>16 significance, which is the P value or the confidence</p> <p>17 intervals.</p> <p>18 Q (By Mr. Williams) With respect to the issue of power,</p> <p>19 you said you needed to get to 931 cases, right?</p> <p>20 MS. PARFITT: Objection; form.</p> <p>21 THE WITNESS: I calculated 91-- 931</p> <p>22 for an individual study.</p> <p>23 Q (By Mr. Williams) And in these cases, if you combine the</p> <p>24 cohort studies, the total number of cases, they are far</p> <p>25 in excess of that number, right?</p>	<p>1 to have lower relative risk is because of the less</p> <p>2 accuracy in collecting the exposure.</p> <p>3 It tends to reduce the point estimate, which is the</p> <p>4 relative risk, if the exposure data is not collected with</p> <p>5 as much refinement as you can see in-- as we've seen in</p> <p>6 some of the other studies.</p> <p>7 Q (By Mr. Williams) Why would it reduce the number rather</p> <p>8 than raise the number?</p> <p>9 Couldn't it do either?</p> <p>10 A I am not sure exactly why, but it tends to do that-- by</p> <p>11 having incomplete information about an exposure, it tends</p> <p>12 to lower the relative risk.</p> <p>13 Q Can you point us to any treatise, any study, any analysis</p> <p>14 that makes that point?</p> <p>15 A Yes.</p> <p>16 Q That you just made?</p> <p>17 A Yes.</p> <p>18 Q Go ahead.</p> <p>19 A I have a reference.</p> <p>20 Q And then I promise we'll take a break.</p> <p>21 A Flegal, Brownie, and Haas, so Reference No. 45--</p> <p>22 Q And you are referring to Reference No. 45 from your</p> <p>23 report?</p> <p>24 A Yes, Reference No. 45.</p> <p>25 MS. PARFITT: Counsel, with your</p>

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<p>1 permission, I will hand her my--</p> <p>2 MR. WILLIAMS: Please.</p> <p>3 Q (By Mr. Williams) For the record, are you looking,</p> <p>4 Dr. McTiernan, to the portion of the Flegal, F-L-E-G-A-L,</p> <p>5 study, Item No. 45 on your reference list, to try to find</p> <p>6 something that supports your conclusion that a lack of--</p> <p>7 I can't remember how you put it, but a lack of sufficient</p> <p>8 questions in a cohort study leads to a lower risk ratio?</p> <p>9 A So I'll read from the abstract, the first two sentences,</p> <p>10 "In epidemiologic studies individuals may be</p> <p>11 misclassified with respect to exposure to a risk factor</p> <p>12 for disease.</p> <p>13 "Such misclassification causes the relative risk of</p> <p>14 disease associated with exposure in the population to be</p> <p>15 biased toward the null value."</p> <p>16 Q And what is it that you believe caused people-- strike</p> <p>17 that.</p> <p>18 I take it you conclude here that the cohort studies</p> <p>19 somehow misclassified some of the women who were</p> <p>20 participating in the study?</p> <p>21 A In the Nurses' Health Study women were asked in 1982, at</p> <p>22 one point, whether they used these products, and it was</p> <p>23 never updated, and it did not ask about their lifetime</p> <p>24 use before that.</p> <p>25 The Women's Health Initiative asked if they had ever</p>	<p>1 At the bottom of Page 28, the last sentence that</p> <p>2 carries over, you wrote, "It should be noted that ovarian</p> <p>3 talc particle burden may not be influenced by number of</p> <p>4 applications of perineal talc usage, and therefore the</p> <p>5 typical dose response relationship may not be necessary</p> <p>6 for establishing causality between perineal talcum powder</p> <p>7 product use and the risk for ovarian cancer."</p> <p>8 What's the basis for that statement?</p> <p>9 A I think I addressed that a little bit this morning, that</p> <p>10 if a woman is exposed to perineal talc and it moves up to</p> <p>11 the fallopian tube or ovarian area, all she would need is</p> <p>12 potentially one dose to then set up inflammation.</p> <p>13 The more that she's exposed to, that suggests the</p> <p>14 more likelihood of having the talc move up to that area,</p> <p>15 so we do look at dose responses to help support this</p> <p>16 association, but it still seems possible that a smaller</p> <p>17 number of doses could still increase risk.</p> <p>18 The reference that I used here, 64, Heller, do we</p> <p>19 have that available?</p> <p>20 (Exhibit No. 18 marked</p> <p>21 for identification.)</p> <p>22</p> <p>23 Q (By Mr. Williams) And we will mark the Heller study as</p> <p>24 Exhibit No. 18.</p> <p>25 If you could, just point me to the page that you're</p>
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<p>1 used it when they entered the study, so that was between</p> <p>2 1992 and 1996.</p> <p>3 It was not updated either.</p> <p>4 It didn't have a full lifetime exposure collected,</p> <p>5 so really you only have one point in time for those two.</p> <p>6 One of them-- one of them asked about years of use</p> <p>7 and one asked about frequency, but neither asked about</p> <p>8 both.</p> <p>9 This is a typical underestimate of exposure when</p> <p>10 you're asking people just at one point in time and not</p> <p>11 updating and not going back in time.</p> <p>12 Q Anything else you want to add?</p> <p>13 A No.</p> <p>14 MR. WILLIAMS: Let's take a break.</p> <p>15 VIDEOGRAPHER: Going off the record,</p> <p>16 the time is 3:19 p.m.</p> <p>17 (Recess 3:19 to 3:39 p.m.)</p> <p>18</p> <p>19 VIDEOGRAPHER: We are back on the</p> <p>20 record. This is the start of Media 4. The time is 3:39</p> <p>21 p.m.</p> <p>22 Q (By Mr. Williams) Dr. McTiernan, do you have Exhibit</p> <p>23 No. 2 in front of you, your report?</p> <p>24 A Yes.</p> <p>25 Q Could you turn to Page 28.</p>	<p>1 referring to.</p> <p>2 A So, yes, if you look at-- just looking at Table No. 1,</p> <p>3 this is 12 women who reported talc use.</p> <p>4 You can see the talc counts weren't necessarily</p> <p>5 correlated with the lifetime talc applications, and this</p> <p>6 is estimated by a woman's report.</p> <p>7 So even women that have a smaller number of</p> <p>8 applications could have a very high talc count.</p> <p>9 Q Have you finished your answer?</p> <p>10 A Yes.</p> <p>11 Q Couldn't that very high talc count be as a result of the</p> <p>12 fact that talc is all over the environment, not just from</p> <p>13 talcum powder but from things we eat, places we go,</p> <p>14 contamination?</p> <p>15 Couldn't it be explained by that?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 THE WITNESS: It seems like a likely</p> <p>18 way for talc to be present in the ovaries is through</p> <p>19 movement up through the genital tract.</p> <p>20 There is some data suggesting that, yes, talc could</p> <p>21 migrate through the lymph system, but there's much more</p> <p>22 data showing that particles can move-- inert particles</p> <p>23 can move through the genital tract up through the</p> <p>24 fallopian tubes and to the ovaries in both animals and</p> <p>25 humans.</p>

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<p>1 Q (By Mr. Williams) Do you remember that the Heller study</p> <p>2 looked at groups of women that both used talcum powder in</p> <p>3 the perineal area and women who did not?</p> <p>4 A Yes. It was about half and half, and--</p> <p>5 Q Hold on. Let me ask the question.</p> <p>6 A Sorry.</p> <p>7 Q You do remember that it looked at both groups of women,</p> <p>8 those who used talc and those who did not, correct?</p> <p>9 A Yes.</p> <p>10 Q And then it looked at their ovaries to determine which</p> <p>11 ones had any evidence of talcum powder.</p> <p>12 Do you remember that?</p> <p>13 A Yes.</p> <p>14 Q And do you remember that the Heller study concluded that</p> <p>15 there were more women who had talcum powder in their</p> <p>16 ovaries who had never used talcum powder in the perineal</p> <p>17 area than there were women who had talc in their ovaries</p> <p>18 who had reported use of talcum powder in the perineal</p> <p>19 area?</p> <p>20 Do you recall that?</p> <p>21 MS. PARFITT: Objection.</p> <p>22 THE WITNESS: What I see in the table</p> <p>23 is a one point different, five versus six.</p> <p>24 They were able then to contact the mothers of these</p> <p>25 women to find out whether the women had been exposed as</p>	<p>1 their genital area that she didn't record, she didn't</p> <p>2 recall.</p> <p>3 Q You're speculating now, aren't you?</p> <p>4 MS. PARFITT: Objection.</p> <p>5 Q (By Mr. Williams) Are you not speculating right now?</p> <p>6 A I don't know. They don't have data saying that the woman</p> <p>7 misrepresented.</p> <p>8 Q What we do have data on is the ages of the women who had</p> <p>9 talc in their ovaries, correct?</p> <p>10 A Yes.</p> <p>11 Q And who were part of this study, right?</p> <p>12 A Yes.</p> <p>13 Q The notion that the fact that they were diapered as</p> <p>14 babies with talcum powder could be an explanation for how</p> <p>15 they had talc in their ovaries doesn't hold up, does it,</p> <p>16 if the ages of the women are, with two exceptions, people</p> <p>17 who are in their 60s and 50s and 40s, right?</p> <p>18 MS. PARFITT: Objection; form,</p> <p>19 misstates the data.</p> <p>20 THE WITNESS: I don't know if we have</p> <p>21 data that can show that, but if talc has migrated up and</p> <p>22 is in the peritoneal area, it sits there. I don't know</p> <p>23 how it would be removed.</p> <p>24 It doesn't seem implausible to me that it could</p> <p>25 remain there for years.</p>
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<p>1 babies, if they had been diapered with talc, and you</p> <p>2 could see quite a few-- three additional that did have</p> <p>3 genital exposure from talc use as babies.</p> <p>4 Q (By Mr. Williams) Dr. McTiernan, what is the latency</p> <p>5 period for ovarian cancer?</p> <p>6 A It's decades, so it's thought to be-- it could be 30, 40</p> <p>7 years.</p> <p>8 Q Isn't it 20 or 30 years?</p> <p>9 MS. PARFITT: Objection; form.</p> <p>10 THE WITNESS: It's not clear if it's</p> <p>11 exactly that, but it could be much longer.</p> <p>12 Q (By Mr. Williams) Well, take a look at the ages of the</p> <p>13 women in Table No. 2.</p> <p>14 Do you see those ages?</p> <p>15 Wouldn't those women have had to have been diapered</p> <p>16 in their 30s and 40s, by your analysis?</p> <p>17 A No, I see one woman is 59, so that would have been a long</p> <p>18 period.</p> <p>19 One is 40.</p> <p>20 One is 64.</p> <p>21 Q If a woman were 59 and the latency period were 40 years,</p> <p>22 that would mean that she would have had to have been</p> <p>23 diapered when she was 19, right?</p> <p>24 A The latency could have been longer in some.</p> <p>25 There's also a possibility of other exposure to</p>	<p>1 Q (By Mr. Williams) Do you have any opinion on how long</p> <p>2 talc particles stay in a woman's ovary, assuming it can</p> <p>3 get to an ovary?</p> <p>4 A I have no data to show me one way or the other.</p> <p>5 Q What we do know from the Heller study though is in Table</p> <p>6 No. 3 for those women who reported talc use, five of the</p> <p>7 12 had talc in their ovary, correct?</p> <p>8 A That's correct.</p> <p>9 Q And six of the women, who reported no talc use, six of</p> <p>10 the 12 had talc in their ovaries, correct?</p> <p>11 A That's correct.</p> <p>12 Q Now, you cited Heller as a basis for-- strike that.</p> <p>13 You criticized the cohort studies earlier today for</p> <p>14 asking only at one point in time whether women used</p> <p>15 talcum powder.</p> <p>16 Do you recall that testimony?</p> <p>17 A Yes, in the sense that it may underreport by asking about</p> <p>18 one period in time.</p> <p>19 Q But you also just testified a few moments ago and you</p> <p>20 testified earlier today that one-time exposure is</p> <p>21 sufficient to support the conclusion that talc causes</p> <p>22 ovarian cancer, right?</p> <p>23 A I don't recall saying that, and I did say that-- I</p> <p>24 thought I just said that the women may not have</p> <p>25 remembered using it.</p>



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<p>1 The ones that said they didn't, they may have not</p> <p>2 remembered, and that is underreporting.</p> <p>3 Q But wouldn't asking the question whether-- one time</p> <p>4 whether a woman ever used talcum powder be enough to give</p> <p>5 the cohort studies the ability to analyze whether there</p> <p>6 was an overall statistically significant association, if</p> <p>7 in fact one existed, given your testimony that all it</p> <p>8 takes is one exposure?</p> <p>9 A I think-- sorry, are you talking about my testimony of</p> <p>10 one exposure in order to cause ovarian cancer?</p> <p>11 Q Yes.</p> <p>12 A There may be other reasons women could say it could not</p> <p>13 report use of talc-- they may not remember it.</p> <p>14 They may not feel comfortable reporting it.</p> <p>15 In these cohort studies there were some subjects</p> <p>16 that were not included because they didn't report use.</p> <p>17 One of the cohort studies didn't include about 500</p> <p>18 women because they didn't have information, they didn't</p> <p>19 answer the question.</p> <p>20 Q You are speculating now, aren't you?</p> <p>21 MS. PARFITT: Objection; form.</p> <p>22 THE WITNESS: We can look at the</p> <p>23 cohort studies to see what the numbers were that didn't</p> <p>24 remember.</p> <p>25 Q (By Mr. Williams) Is it your testimony that use of--</p>	<p>1 THE WITNESS: I would have to look at</p> <p>2 the question again, but they were asked at one point if</p> <p>3 they were using, and--</p> <p>4 Q (By Mr. Williams) Weren't they asked in some of the</p> <p>5 cohort studies whether they ever used talcum powder?</p> <p>6 A One of them did and one didn't, so I would have to look</p> <p>7 back.</p> <p>8 Q Regardless of which one is which, which one said, "Look</p> <p>9 back" or which one side, "Are you currently using," isn't</p> <p>10 the point that if talcum powder use in the perineal area</p> <p>11 is a habitual thing that women did and do after</p> <p>12 showering, after exercising-- after being out in the</p> <p>13 world, if they're hot, if it is something that is</p> <p>14 habitually done, then is there any reason to believe that</p> <p>15 when a woman reports that she has used talcum powder,</p> <p>16 that she's only done it one time?</p> <p>17 MS. PARFITT: Objection; form.</p> <p>18 THE WITNESS: I don't know the answer</p> <p>19 to that. I haven't seen the data.</p> <p>20 Q (By Mr. Williams) Earlier today you were asked questions</p> <p>21 about cohort study methodology, and I believe you said</p> <p>22 that one of the problems with the cohort studies is that</p> <p>23 they ask about a lot of substances and not just talcum</p> <p>24 powder.</p> <p>25 Do you recall saying that?</p>
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<p>1 strike that.</p> <p>2 Do you have an understanding, as you sit there, as</p> <p>3 to whether or not use of talcum powder in the perineal</p> <p>4 area is a habitual activity or something that is done</p> <p>5 once and never again?</p> <p>6 A I don't think we have data showing one way or the other.</p> <p>7 Q Do you believe that there are no studies that talk at all</p> <p>8 about whether or not this is a habit, the use-- and by</p> <p>9 "this," I mean the use of talcum powder in the perineal</p> <p>10 area?</p> <p>11 A I didn't review that.</p> <p>12 The studies talked about what proportion of people</p> <p>13 were using talc at the time that they were interviewed.</p> <p>14 I noticed the Women's Health Initiative is 40</p> <p>15 percent were using it. I think Nurses' Health Study was</p> <p>16 about 50 percent using it, whereas the sister study, a</p> <p>17 very small percent, they were interviewed more recently</p> <p>18 or they answered questions more recently.</p> <p>19 I don't recall the studies determining whether</p> <p>20 somebody had used it once versus several times or a</p> <p>21 habitual use versus nonhabitual use.</p> <p>22 Q So the cohort studies that started in 1982, is it your</p> <p>23 testimony that those women started using talcum powder in</p> <p>24 1982?</p> <p>25 MS. PARFITT: Objection.</p>	<p>1 A Yes.</p> <p>2 Q And isn't it true-- strike that.</p> <p>3 Isn't it true that a number of the cohort studies</p> <p>4 ask about multiple substance-- strike that.</p> <p>5 Isn't it true that a number of the case-control</p> <p>6 studies ask about a number of substances?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 THE WITNESS: Without having the</p> <p>9 questionnaires for all of the case-control studies, I</p> <p>10 can't answer about exactly what they asked about other</p> <p>11 variables.</p> <p>12 Certainly case-control studies, many of the ones</p> <p>13 included, asked about several different potential</p> <p>14 exposures in relation to ovarian cancer.</p> <p>15 They were designed to look at ovarian cancer.</p> <p>16 The cohort studies, however, were designed to look</p> <p>17 at exposures related to cardiovascular disease, various</p> <p>18 cancers, osteoporosis, arthritis, cognition, so there are</p> <p>19 many, many different forms that these women filled out,</p> <p>20 and the Women's Health Initiative in the cohort study,</p> <p>21 they were completing forms every year with different</p> <p>22 types of information collected.</p> <p>23 At baseline, which is the only time when talc was</p> <p>24 collected, they had multiple forms that they had to</p> <p>25 complete.</p>

<p style="text-align: right;">Page 242</p> <p>1 Q (By Mr. Williams) What is it about asking about multiple</p> <p>2 substances and not just talcum powder that makes that</p> <p>3 practice in some cohort studies unreliable, in your view?</p> <p>4 A It could make it unreliable, but it certainly is fatigue,</p> <p>5 how many questions can somebody answer accurately.</p> <p>6 The cohort studies were self-administered forms, so</p> <p>7 the woman had no prompting, no additional help with</p> <p>8 remembering.</p> <p>9 The two studies that I could find, the actual</p> <p>10 questionnaire, the Nurses' Health Study and the Women's</p> <p>11 Health Initiative, they're very short and simple</p> <p>12 questions without going through any information about</p> <p>13 what they might have been doing at different time points</p> <p>14 in their life.</p> <p>15 The Nurses' Health Study had one little question</p> <p>16 about five categories to fill in, so something that's</p> <p>17 that short can underestimate the level of exposure.</p> <p>18 Q Does being fatigued make a woman check the box saying</p> <p>19 that she used talc or does it make her not check the box</p> <p>20 saying that she used talc?</p> <p>21 A I don't know.</p> <p>22 Q Then what does fatigue have to do with it?</p> <p>23 A If it makes the result less accurate, whichever way it</p> <p>24 goes, the misclassification, as we just talked about,</p> <p>25 that then can drive the relative risk lower towards the</p>	<p style="text-align: right;">Page 244</p> <p>1 not all statistically significant, right?</p> <p>2 MS. PARFITT: Objection; form,</p> <p>3 misstates her testimony.</p> <p>4 THE WITNESS: When you look at studies</p> <p>5 that were small, the smaller, older studies tended to be</p> <p>6 less likely to have statistical significance, and the</p> <p>7 newer, larger studies were more likely to be</p> <p>8 statistically significant.</p> <p>9 Q (By Mr. Williams) You agree that simply combining data</p> <p>10 into meta or pooled analyses does not entirely eliminate</p> <p>11 the underlying flaws of the individual studies, true?</p> <p>12 A Yes, when you combine data, then the individual study's</p> <p>13 data still stand.</p> <p>14 What you're doing by combining data is smoothing out</p> <p>15 variability across studies and increasing sample size.</p> <p>16 Q Take a look at the Berge study, 16A, that we were looking</p> <p>17 at earlier, and take a look at Figure No. 2.</p> <p>18 That's the Forest plot, right?</p> <p>19 A Yes.</p> <p>20 Q This breaks out the case-control and the cohort studies</p> <p>21 analyzed for the meta-analysis, right?</p> <p>22 A Yes.</p> <p>23 Q There's a combined relative risk for the case-controls</p> <p>24 and the cohort combined, and that is the 1.22 indicated</p> <p>25 at the bottom of the table, right?</p>
<p style="text-align: right;">Page 243</p> <p>1 null.</p> <p>2 Q But it also can drive it higher, right, depending on</p> <p>3 which way it goes?</p> <p>4 MS. PARFITT: Objection; form.</p> <p>5 THE WITNESS: Not usually from this</p> <p>6 classification. It usually drives it towards the null.</p> <p>7 Q (By Mr. Williams) Your opinion that perineal talc use</p> <p>8 can cause ovarian cancer is based on what you describe as</p> <p>9 a statistically significant elevated risk, right?</p> <p>10 A That's correct, overall, looking at the meta-analysis and</p> <p>11 the pooled analysis.</p> <p>12 Q And that statistically significant elevated risk estimate</p> <p>13 is in combined data in the meta-analysis, correct?</p> <p>14 A Correct, adding the studies together.</p> <p>15 Q By combining the data, you are referring to meta-analyses</p> <p>16 and pooled analyses, right?</p> <p>17 A Yes.</p> <p>18 Q Your opinion of that combined data is based upon</p> <p>19 statistical significance, correct?</p> <p>20 A Partly. It's based also on consistency across the</p> <p>21 individual studies and also the effect size consistently</p> <p>22 being elevated in most of the studies.</p> <p>23 Q You do agree that when you do not combine the data,</p> <p>24 meaning when you look at the individual sourced studies</p> <p>25 from which the meta-analyses are performed, the data is</p>	<p style="text-align: right;">Page 245</p> <p>1 A That's correct.</p> <p>2 MR. LOCKE: Excuse me, can we just</p> <p>3 take a quick break?</p> <p>4 VIDEOGRAPHER: Going off the record,</p> <p>5 the time is 3:59 p.m. Please stand by.</p> <p>6 (Recess 3:59 to 4:00 p.m.)</p> <p>7</p> <p>8 VIDEOGRAPHER: We are back on the</p> <p>9 record. The time is 4 p.m.</p> <p>10 Q (By Mr. Williams) Dr. McTiernan, do you have the Berge</p> <p>11 study, Exhibit No. 16A, in front of you?</p> <p>12 A Yes.</p> <p>13 Q And you are looking at the Forest plot?</p> <p>14 A Yes.</p> <p>15 Q I would like to focus you on the case-control studies.</p> <p>16 I have counted the total number there.</p> <p>17 I count 24 total.</p> <p>18 Is that what you count?</p> <p>19 A Yes.</p> <p>20 Q If we look at those studies that have a confidence</p> <p>21 interval that crosses over 1.0, there are 12 of them,</p> <p>22 correct?</p> <p>23 A Yes, the earlier studies do.</p> <p>24 Q And that means that there are 12 that are not</p> <p>25 statistically significant, correct?</p>

<p style="text-align: right;">Page 246</p> <p>1 A Yes.</p> <p>2 Q So as between just the case-control studies, the 24</p> <p>3 listed here, at best only 50 percent of them or 12 of</p> <p>4 them reflect a statistically significant association,</p> <p>5 true?</p> <p>6 MS. PARFITT: Objection; form.</p> <p>7 THE WITNESS: And, again, that's</p> <p>8 largely based on sample size.</p> <p>9 The earlier studies tended to be smaller than the</p> <p>10 older ones-- sorry, than the more recent ones, which the</p> <p>11 sample size drives statistical significance.</p> <p>12 Q (By Mr. Williams) It is accurate that 12 of the</p> <p>13 case-control studies did not find a statistically</p> <p>14 significant association, true or not true?</p> <p>15 MS. PARFITT: Objection; form, asked</p> <p>16 and answered.</p> <p>17 THE WITNESS: The sample size drives</p> <p>18 the statistical significance, and the larger, more recent</p> <p>19 studies, were more likely to be statistically</p> <p>20 significant.</p> <p>21 The smaller, older studies, were more likely to be</p> <p>22 not statistically significant.</p> <p>23 Q (By Mr. Williams) The combined risk estimate for the 24</p> <p>24 case-control studies came out to a statistically</p> <p>25 significant number, correct?</p>	<p style="text-align: right;">Page 248</p> <p>1 significant?</p> <p>2 MS. PARFITT: Objection; form, asked</p> <p>3 and answered.</p> <p>4 Q (By Mr. Williams) Am I right?</p> <p>5 A My response is that they showed different results, not</p> <p>6 just the statistical significance being different, but</p> <p>7 the point estimate is different.</p> <p>8 Q Let me put it this way:</p> <p>9 On the question of statistical significance, yes or</p> <p>10 no, are the results-- the combined results of the</p> <p>11 case-controls consistent with the combined results on the</p> <p>12 cohort studies or not, yes or no?</p> <p>13 MS. PARFITT: Objection; form, asked</p> <p>14 and answered.</p> <p>15 THE WITNESS: So I think I answered</p> <p>16 before, the statistical significance was different and</p> <p>17 they showed different results.</p> <p>18 Q (By Mr. Williams) And the different results that they</p> <p>19 showed was that one, the cohorts, was not statistically</p> <p>20 significant, and the case-controls, overall, were</p> <p>21 statistically significant, correct?</p> <p>22 MS. PARFITT: Objection; form, asked</p> <p>23 and answered multiple times.</p> <p>24 THE WITNESS: So I answered more</p> <p>25 fully, I think, than just statistical significance.</p>
<p style="text-align: right;">Page 247</p> <p>1 A That's correct.</p> <p>2 Q The combined risk estimate for the cohort studies, on the</p> <p>3 other hand, did not come out to a statistically</p> <p>4 significant number, right?</p> <p>5 A That's correct.</p> <p>6 Q Can we agree that on the question of statistical</p> <p>7 significance, the combined risk estimate for the</p> <p>8 case-control studies are not consistent with the combined</p> <p>9 risk estimate for the cohort studies?</p> <p>10 MS. PARFITT: Objection; form, asked</p> <p>11 and answered, misstates her prior testimony.</p> <p>12 You may answer.</p> <p>13 THE WITNESS: The combined cohort</p> <p>14 study not only was not significant, the relative risk was</p> <p>15 1.02.</p> <p>16 Q (By Mr. Williams) I don't believe you answered my</p> <p>17 question.</p> <p>18 My question is:</p> <p>19 Can we agree that a question of statistical</p> <p>20 significance, just that question, the combined risk</p> <p>21 estimate for the case-control studies are not consistent</p> <p>22 with the combined risk estimate for the cohort studies</p> <p>23 because for the cohort studies the result was not</p> <p>24 statistically significant, and for the case-control</p> <p>25 studies the combined estimate was statistically</p>	<p style="text-align: right;">Page 249</p> <p>1 I answered both about the relative risk, which is</p> <p>2 the point estimate, and the statistical significance, so</p> <p>3 the point estimate was 1.02 in the cohort studies, not</p> <p>4 statistically significant.</p> <p>5 It was 1.26 in the case-control studies, and that</p> <p>6 was statistically significant.</p> <p>7 Q (By Mr. Williams) Perhaps that's where the issue is.</p> <p>8 For purposes of my question, I am asking you to</p> <p>9 limit your analysis to the question of statistical</p> <p>10 significance.</p> <p>11 Are you with me so far?</p> <p>12 A I understand what you're saying.</p> <p>13 Q With respect to statistical significance, with respect to</p> <p>14 that issue, is it your testimony that the case-control</p> <p>15 studies, which find that there is a statistically</p> <p>16 significant positive odds ratio or relative risk, and the</p> <p>17 cohort studies, which do not collectively have a positive</p> <p>18 relative risk, is it your testimony that those are</p> <p>19 consistent with respect to the issue of statistical</p> <p>20 significance?</p> <p>21 MS. PARFITT: Objection; form, asked</p> <p>22 and answered, hopefully for the last time.</p> <p>23 THE WITNESS: And I think I don't look</p> <p>24 at statistical significance in the same way for a</p> <p>25 relative risk of 1.02 as I do for 1.26, but there is</p>

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<p>1 something remarkable here, is that the upper limit of the</p> <p>2 confidence interval for the cohort studies is almost up</p> <p>3 to the relative risk for the case-control studies, so the</p> <p>4 statistical significance test tells us the relative risk</p> <p>5 could be as high as 1.2, so even though you call it</p> <p>6 nonstatistically significant, it's still within 95</p> <p>7 percent chance that it's up at 1.2.</p> <p>8 Q (By Mr. Williams) Are they both statistically</p> <p>9 significant or not, the case-controls or the-- and the</p> <p>10 cohort studies?</p> <p>11 MS. PARFITT: Objection; form, asked</p> <p>12 and answered.</p> <p>13 Counsel, I do believe she is trying to answer the</p> <p>14 question.</p> <p>15 This is about the tenth time.</p> <p>16 Q (By Mr. Williams) You may answer.</p> <p>17 MS. PARFITT: Give your response</p> <p>18 again.</p> <p>19 THE WITNESS: I think I'm sorry, but I</p> <p>20 don't think of something as just looking at the</p> <p>21 statistical significance.</p> <p>22 I always look at both the relative risk and the</p> <p>23 statistical significance.</p> <p>24 Repeating, the relative risk is only 1.2 for the</p> <p>25 cohort studies.</p>	<p>1 Just so we can remember, my question to you is:</p> <p>2 Are you unable to answer my question because I am</p> <p>3 limiting the question to talk about statistical</p> <p>4 significance and whether those findings are consistent or</p> <p>5 inconsistent?</p> <p>6 MS. PARFITT: Objection; form.</p> <p>7 Answer his question.</p> <p>8 You have answered multiple times.</p> <p>9 THE WITNESS: I think my answer is I</p> <p>10 don't look at just statistical significance. I look at</p> <p>11 point estimate as well.</p> <p>12 Q (By Mr. Williams) Are you an expert in asbestos?</p> <p>13 A No, I'm not an expert in asbestos.</p> <p>14 Q Are you an expert in geology?</p> <p>15 A No.</p> <p>16 Q Mineralogy?</p> <p>17 A No.</p> <p>18 Q Can you distinguish between an asbestiform fiber on the</p> <p>19 one hand and a cleavage fragment on the other?</p> <p>20 A No.</p> <p>21 Q Can you distinguish between an asbestiform and a</p> <p>22 nonasbestiform fiber?</p> <p>23 A No.</p> <p>24 Q Are you an expert in microscopy?</p> <p>25 A In which?</p>
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<p>1 The confidence interval includes one, so that would</p> <p>2 be considered not statistically significant, but it</p> <p>3 ranges up to 1.2, which means the relative risk could be</p> <p>4 as high as 1.2 for the cohort studies.</p> <p>5 Q (By Mr. Williams) You're speculating; are you not?</p> <p>6 MS. PARFITT: Objection; form.</p> <p>7 THE WITNESS: I'm interpreting--</p> <p>8 MS. PARFITT: Misstates your</p> <p>9 testimony.</p> <p>10 THE WITNESS: I am interpreting what</p> <p>11 the 95 percent confidence intervals mean.</p> <p>12 It's not a speculation.</p> <p>13 Q (By Mr. Williams) Is the answer that you are not able to</p> <p>14 answer my question as phrased when I limit the question</p> <p>15 to an analysis of statistical significance?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 She has answered your question completely.</p> <p>18 Let's move on, Mr. Williams.</p> <p>19 You are not going to get a different answer.</p> <p>20 You can use up the remaining of your time if you</p> <p>21 would like, but she has answered the question.</p> <p>22 Q (By Mr. Williams) You may answer, Doctor.</p> <p>23 MS. PARFITT: You are asking questions</p> <p>24 10, 15 times--</p> <p>25 Q (By Mr. Williams) You may answer.</p>	<p>1 Q Microscopy.</p> <p>2 A No.</p> <p>3 Q Are you qualified to analyze bulk samples of baby powder</p> <p>4 using different types of microscopes?</p> <p>5 A No, I'm not.</p> <p>6 Q Are you qualified to perform any of the following tests</p> <p>7 for purposes of analyzing a talcum powder sample:</p> <p>8 X-ray defraction?</p> <p>9 A Are you going to list them or do you want me to say</p> <p>10 "no"--</p> <p>11 Q You can answer them one at a time.</p> <p>12 A No.</p> <p>13 Q Polarized light microscopy?</p> <p>14 A No.</p> <p>15 Q Transmission electron microscopy?</p> <p>16 A No.</p> <p>17 Q In your work do you review and analyze other people's</p> <p>18 defraction patterns or readouts or images or other</p> <p>19 results of microscopic testing for-- of talcum powder for</p> <p>20 asbestos, the presence of asbestos?</p> <p>21 A Are you talking about looking at the details of their</p> <p>22 sampling?</p> <p>23 Q Correct.</p> <p>24 A To determine the methods? No, I would not do that.</p> <p>25 Q Regardless of the method, have you ever personally tested</p>

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<p>1 any talcum powder product for asbestos?</p> <p>2 A No.</p> <p>3 Q Have you ever been to a talc mine?</p> <p>4 A No.</p> <p>5 Q How about a talc mill?</p> <p>6 A No.</p> <p>7 Q Do you know how talc is selected from a mine, sorted,</p> <p>8 sterilized, processed before it is ever put into a bottle</p> <p>9 of Johnson's Baby Powder?</p> <p>10 A No, I don't.</p> <p>11 Q Do you know what methods are used to test the cosmetic</p> <p>12 talc in Johnson's Baby Powder products for asbestos?</p> <p>13 A Are you talking about what your company methods are to</p> <p>14 test?</p> <p>15 Q Whether it was the company's methods or someone else's--</p> <p>16 A No.</p> <p>17 Q Do you know how many methods were used over the years to</p> <p>18 test cosmetic talc in Johnson's Baby Powder products for</p> <p>19 asbestos?</p> <p>20 A In some of the documents I've reviewed, I have seen</p> <p>21 mention of several types, but I couldn't-- I am not an</p> <p>22 expert in them.</p> <p>23 Q Do you know how often cosmetic talc, in Johnson's Baby</p> <p>24 Powder products, were tested for asbestos?</p> <p>25 A By anybody, I don't know.</p>	<p>1 2014 have shown that present-day talcum powder products</p> <p>2 include several types of asbestos, and you cite two</p> <p>3 sources, right?</p> <p>4 A Yes.</p> <p>5 Q And those are Gordon 2014 and Blount 1991?</p> <p>6 A That's correct.</p> <p>7 Q You also cite to Exhibit No. 47 of the deposition of</p> <p>8 Imerys witness Julie Pier, P-I-E-R.</p> <p>9 Do you remember that?</p> <p>10 A Yes.</p> <p>11 Q And to Exhibit No. 24 to the deposition of Johnson &amp;</p> <p>12 Johnson witness John Hopkins, correct?</p> <p>13 A Yes.</p> <p>14 Q You also have cited to five litigation reports. Those</p> <p>15 are referenced as 79 to 83, which were prepared by</p> <p>16 Dr. William Longo, right?</p> <p>17 A Yes.</p> <p>18 Q Are you in fact relying upon Gordon 2014, Blount 1991,</p> <p>19 Pier Exhibit No. 47, Hopkins Exhibit No. 24, and the five</p> <p>20 Longo reports for your opinion that asbestos has been</p> <p>21 found specifically in Johnson's Baby Powder products?</p> <p>22 A I would have to look at Gordon again to see what that</p> <p>23 said about Johnson &amp; Johnson.</p> <p>24 Blount did identify one of the components as baby</p> <p>25 powder.</p>
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<p>1 Q Is it your opinion that at one point in time or another,</p> <p>2 Johnson's Baby Powder products contained asbestos?</p> <p>3 I think you told us you believe that's true,</p> <p>4 correct?</p> <p>5 A Yes, that is my opinion.</p> <p>6 Q I will rephrase.</p> <p>7 Is it your opinion that Johnson's Baby Powder</p> <p>8 products sold today contain asbestos?</p> <p>9 MS. PARFITT: Objection; form, asked</p> <p>10 and answered.</p> <p>11 THE WITNESS: I believe from the</p> <p>12 evidence I've seen, that there was asbestos as recently</p> <p>13 as samples tested in the 2000s.</p> <p>14 I don't know for 2019.</p> <p>15 I haven't seen any reports on that.</p> <p>16 Q (By Mr. Williams) And am I right-- if you take a look at</p> <p>17 Page 57 of your report, Exhibit No. 2, and I'm referring</p> <p>18 you to the bottom of the page, the last paragraph, does</p> <p>19 that paragraph summarize your opinion that asbestos has</p> <p>20 been found in Johnson's Baby Powder products</p> <p>21 specifically?</p> <p>22 A So are you talking about the whole paragraph?</p> <p>23 Q Correct.</p> <p>24 You mention Reference No. 75 and Reference No. 76 as</p> <p>25 supporting the idea that published data as recently as</p>	<p>1 Pier and Hopkins were Johnson &amp; Johnson products,</p> <p>2 and Longo tested products from-- my understanding from</p> <p>3 the report, from Johnson &amp; Johnson.</p> <p>4 Q Other than the materials that we just identified, are you</p> <p>5 relying on anything else to support your opinion that</p> <p>6 asbestos has been found specifically in Johnson's Baby</p> <p>7 Powder products?</p> <p>8 A No.</p> <p>9 Q "No," you are not relying on anything else?</p> <p>10 A No, I'm not.</p> <p>11 Q Are you aware that at the time they authored the article</p> <p>12 identified as Reference No. 75 -- that's the Gordon 2014</p> <p>13 report -- that each of the three authors had been a paid</p> <p>14 expert for the plaintiffs' lawyers in talcum powder</p> <p>15 litigation?</p> <p>16 A I believe they said that in their disclosures.</p> <p>17 Do we have 75 available?</p> <p>18 Q While they are looking for that, Doctor, do you recall</p> <p>19 whether they identified in the Gordon 2014 article, and</p> <p>20 by "they," I mean the authors, did they identify whether</p> <p>21 they were plaintiff experts; that is, experts retained by</p> <p>22 plaintiffs in litigation.</p> <p>23 A It says, "Attorneys for the litigation process."</p> <p>24 Q It does not say whether it's Plaintiff or Defendant,</p> <p>25 correct?</p>



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<p>1 A I don't see it here--</p> <p>2 Q I'm sorry, what was--</p> <p>3 A It doesn't say for the plaintiff or the defense. It</p> <p>4 doesn't say which.</p> <p>5 Q Do you know, one way or the other, whether the product</p> <p>6 tested in that article was Johnson's Baby Powder?</p> <p>7 A No, I can't recall if I saw it.</p> <p>8 My paragraph didn't talk about Johnson &amp; Johnson,</p> <p>9 just talked about talcum powder products.</p> <p>10 Q Okay. Let me ask you to assume, for purposes of my next</p> <p>11 question, that the product that is referred to in the</p> <p>12 Gordon article was not Johnson's Baby Powder.</p> <p>13 Will you make that assumption for purposes only of</p> <p>14 my question?</p> <p>15 A Okay.</p> <p>16 Q Okay. How would an article about a different talcum</p> <p>17 powder product than the ones that are at issue in this</p> <p>18 case support your opinion that perineal use of Johnson's</p> <p>19 Baby Powder products cause ovarian cancer?</p> <p>20 MS. PARFITT: Objection; form.</p> <p>21 THE WITNESS: My opinion was-- from my</p> <p>22 report, my opinion was that talcum powder product use of</p> <p>23 any source increases risk of ovarian cancer.</p> <p>24 Q (By Mr. Williams) Okay. With respect to the Blount</p> <p>25 article, 1991, Reference No. 76 in your report is the</p>	<p>1 Q Let me ask you about John Hopkins.</p> <p>2 You referenced having read some documents that bore</p> <p>3 his name, correct?</p> <p>4 A Yes.</p> <p>5 Q Let's mark as Exhibit No. 19 a document that I believe</p> <p>6 was Reference No. 78 in your report.</p> <p>7 (Exhibit No. 19 marked</p> <p>8 for identification.)</p> <p>9</p> <p>10 Q (By Mr. Williams) Do you recognize this as the document</p> <p>11 in your report that you cited in support of your opinion</p> <p>12 that talcum powder products contained asbestos?</p> <p>13 A Yes.</p> <p>14 Q It is Exhibit No. 24, you see there, with the little tab,</p> <p>15 to John Hopkins' August 17, 2018 deposition, correct?</p> <p>16 A Okay. Here it says "19."</p> <p>17 Q What says 19?</p> <p>18 A I have Exhibit No. 19 for this one, 24 for the--</p> <p>19 Q Correct.</p> <p>20 Just so you know, for this deposition it's Exhibit</p> <p>21 No. 19.</p> <p>22 For Mr. Hopkins' deposition it was Exhibit No. 24.</p> <p>23 Do you understand?</p> <p>24 A Yes.</p> <p>25 Q Is this one of the documents that Plaintiffs' counsel</p>
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<p>1 article by author A.M. Blount.</p> <p>2 Do you recall that?</p> <p>3 A Yes.</p> <p>4 Q What information from the Blount 1991 article are you</p> <p>5 relying on for your opinion that the contaminated</p> <p>6 products mentioned in that article refer to Johnson's</p> <p>7 Baby Powder products?</p> <p>8 A So there was a table with unidentified samples labelled A</p> <p>9 to O, and I is indicated as-- somewhere it's written as</p> <p>10 baby powder, I believe.</p> <p>11 Then from litigation there was some indication of</p> <p>12 what these different samples were, and so that one was</p> <p>13 identified as Johnson &amp; Johnson Baby Powder.</p> <p>14 Q Did you review the entirety of Dr. Blount's deposition?</p> <p>15 A No. I skimmed part of it. I didn't review-- I skimmed</p> <p>16 part of it. I didn't read the total deposition.</p> <p>17 Q Did you read the part of the deposition where Dr. Blount</p> <p>18 testified that the bottle of Johnson's Baby Powder that</p> <p>19 she brought to the deposition could not possibly be the</p> <p>20 bottle of talc that she identified as Sample No. 1 in her</p> <p>21 1991 article?</p> <p>22 A You mean Sample 1 or Sample I?</p> <p>23 Q Sample I, thank you.</p> <p>24 It's Roman I or I.</p> <p>25 A I didn't read that, no.</p>	<p>1 sent to you without your asking?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: They did send it to me.</p> <p>4 I don't recall if I asked for it or not.</p> <p>5 Q (By Mr. Williams) Do you have any idea if the three</p> <p>6 pages of testing contained in Mr. Hopkins' Exhibit No. 24</p> <p>7 is representative of all the testing that was done on</p> <p>8 Johnson &amp; Johnson talcum powder products?</p> <p>9 A I don't, but I would be concerned about any bottles</p> <p>10 having asbestos in them.</p> <p>11 Q Do you have a problem with the notion that the seller of</p> <p>12 talcum powder products tests for asbestos?</p> <p>13 MS. PARFITT: Objection; form.</p> <p>14 THE WITNESS: Do I have a problem with</p> <p>15 the notion that the seller tests--</p> <p>16 Q (By Mr. Williams) I'll rephrase it.</p> <p>17 A No, I don't have a problem.</p> <p>18 Q And the reason you don't have a problem is that the</p> <p>19 seller of a product could, in all good faith, seek to</p> <p>20 determine whether or not a particular mine where they're</p> <p>21 getting the product contains asbestos, right?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 THE WITNESS: Okay.</p> <p>24 Q (By Mr. Williams) So the mere fact-- what I'm getting at</p> <p>25 is:</p>

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<p>1 The mere fact that a company tests to determine</p> <p>2 whether or not there is asbestos, for example, in a mine</p> <p>3 where they are mining for talcum powder, that fact, in</p> <p>4 and of itself, is not repugnant to you in any way,</p> <p>5 correct?</p> <p>6 A No.</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 Q (By Mr. Williams) It is not repugnant to you, for</p> <p>9 example, for a car company to test whether cars of a</p> <p>10 particular make and model have brakes that work, right?</p> <p>11 A Correct.</p> <p>12 Q The fact that they test for brakes does not mean that the</p> <p>13 brakes do not work, right?</p> <p>14 A Correct.</p> <p>15 Q The fact that they test for brakes doesn't mean that the</p> <p>16 product that is actually sold to people does not have</p> <p>17 brakes that can stop a car, right?</p> <p>18 MS. PARFITT: Objection; form.</p> <p>19 THE WITNESS: There are a couple of</p> <p>20 negatives there. I'm just getting a little confused.</p> <p>21 Q (By Mr. Williams) I will start over.</p> <p>22 The mere fact that a car company tests its makes and</p> <p>23 models to see whether the brakes work does not mean that</p> <p>24 the cars that are ultimately sold have brakes that do not</p> <p>25 work?</p>	<p>1</p> <p>2 Q (By Mr. Williams) Let me show you what we've marked as</p> <p>3 Exhibit No. D-1-- Exhibit No. 20. Pardon me.</p> <p>4 MS. PARFITT: Counsel, I have not seen</p> <p>5 this before.</p> <p>6 Can you represent to us what this is?</p> <p>7 MR. WILLIAMS: I will in a second.</p> <p>8 Q (By Mr. Williams) Have you ever seen this document,</p> <p>9 Dr. McTiernan, what's been marked as Exhibit No. 20?</p> <p>10 A I don't think so-- well--</p> <p>11 Q Did Plaintiffs' counsel provide this to you?</p> <p>12 A I don't recall.</p> <p>13 Q Let me represent to you that this is Exhibit No. D-1,</p> <p>14 D-1, to John Hopkins October 17, 2018 deposition.</p> <p>15 Will you accept that representation?</p> <p>16 A Yes.</p> <p>17 Q You see the tab number that has-- it bears a deposition</p> <p>18 tab number just like your deposition has exhibits with</p> <p>19 tabs?</p> <p>20 A Yes.</p> <p>21 Q Do you see that Exhibit D-1 appears to contain the same</p> <p>22 information as Hopkins' Exhibit No. 24, which you were</p> <p>23 provided by Plaintiffs' counsel, except there's an</p> <p>24 additional column that says "The whole story"?</p> <p>25 A I think there's an awful lot of information here.</p>
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<p>1 A Correct.</p> <p>2 Q Do you know whether this Exhibit No. 24 that's in front</p> <p>3 of you, from Dr. Hopkins, represents final or preliminary</p> <p>4 test results?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: Final or preliminary?</p> <p>7 Can you explain that, meaning-- what do you mean by</p> <p>8 those two?</p> <p>9 Q (By Mr. Williams) Do you know the difference between a</p> <p>10 preliminary test and a final test?</p> <p>11 A I mean, in terms of what it means for the company, I</p> <p>12 don't know what final or preliminary would mean in terms</p> <p>13 of their testing procedures.</p> <p>14 Q Do you know, one way or the other, if any of the results</p> <p>15 were updated or corrected?</p> <p>16 MS. PARFITT: Objection; form.</p> <p>17 THE WITNESS: Updated for a particular</p> <p>18 sample or updated for all of their products?</p> <p>19 Q (By Mr. Williams) Either.</p> <p>20 A I think I'm confused.</p> <p>21 I see what was tested for this, and it says Shower</p> <p>22 to Shower, medicated powder, baby powder, so I would</p> <p>23 assume that that's an actual product.</p> <p>24 (Exhibit No. 20 marked</p> <p>25 for identification.)</p>	<p>1 Q Let's take a couple-- let's take the first one at the top</p> <p>2 of the page.</p> <p>3 Under "The whole story," it says, "Tremolite is not</p> <p>4 asbestos."</p> <p>5 Do you see that?</p> <p>6 A Yes.</p> <p>7 Q And you don't know, as you sit here, whether tremolite is</p> <p>8 or is not asbestos, right?</p> <p>9 MS. PARFITT: Objection; misstates her</p> <p>10 testimony.</p> <p>11 THE WITNESS: I am confused about that</p> <p>12 because IARC states that tremolite is asbestos, so--</p> <p>13 Q (By Mr. Williams) We'll get to that in a minute.</p> <p>14 Is it your testimony that the IARC monograph does</p> <p>15 not make any distinction between a mineral known as</p> <p>16 tremolite and one known as tremolite asbestos?</p> <p>17 MS. PARFITT: Objection; form,</p> <p>18 misstates her testimony.</p> <p>19 THE WITNESS: I don't recall. We</p> <p>20 would have to read it.</p> <p>21 Q (By Mr. Williams) You don't remember one way or another?</p> <p>22 A No.</p> <p>23 Q Do you see the last line on the first page refers to, in</p> <p>24 this same document, Exhibit No. 20 to your deposition,</p> <p>25 D-1 to Dr. Hopkins' deposition, it refers to trace</p>

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<p>1 amounts of fibrous minerals, but "The whole story" column</p> <p>2 indicates that that does not mean asbestos?</p> <p>3 MS. PARFITT: Objection.</p> <p>4 Is that what it says?</p> <p>5 Is that the question?</p> <p>6 Q (By Mr. Williams) Do you see that that's what it says?</p> <p>7 A It says, "Fibrous minerals does not mean asbestos," so--</p> <p>8 is it fibrous talc? That could be carcinogenic as well.</p> <p>9 Is that correct?</p> <p>10 Q Do you know the difference between fibrous talc and</p> <p>11 fibrous minerals?</p> <p>12 A I couldn't distinguish myself. I'm not a mineralogist,</p> <p>13 no.</p> <p>14 Q What's the basis for your testimony?</p> <p>15 I think you were suggesting a moment ago that</p> <p>16 fibrous talc is somehow carcinogenic.</p> <p>17 Is that what you were suggesting?</p> <p>18 A I believe that IARC considers that it could be, so I</p> <p>19 would have to look at the IARC report again to fully</p> <p>20 report.</p> <p>21 Q So the basis for your testimony then is that you believe</p> <p>22 that IARC states that fibrous talc is carcinogenic?</p> <p>23 A Yes, but I need to look at the report again.</p> <p>24 Q Okay. You are relying on five litigation reports</p> <p>25 authored or co-authored by Dr. Longo as part of his paid</p>	<p>1 Q Do you know one way or the other whether the samples that</p> <p>2 Dr. Longo tested were open and unsealed when he received</p> <p>3 them?</p> <p>4 A I don't recall reading that.</p> <p>5 I would have to look at the report again.</p> <p>6 Q Do you know that Dr. Longo did not personally test any of</p> <p>7 the samples he reports on in the litigation documents</p> <p>8 that you relied on in the case?</p> <p>9 MS. PARFITT: Objection; misstates the</p> <p>10 record.</p> <p>11 THE WITNESS: I just read the summary</p> <p>12 report, which looked like his company did the testing.</p> <p>13 Q (By Mr. Williams) Please turn to Page 57 of your report.</p> <p>14 I want to focus your attention on the fourth</p> <p>15 paragraph there that starts with the word "Asbestos."</p> <p>16 A Yes.</p> <p>17 Q Does that paragraph accurately summarize the bases of</p> <p>18 your opinion that asbestos is established as a cause of</p> <p>19 epithelial ovarian cancer?</p> <p>20 A Yes.</p> <p>21 Q You cite the 2011 Camargo, C-A-M-A-R-G-O, and the 2011</p> <p>22 Reid, R-E-I-D, meta-analyses in support of your opinion</p> <p>23 that asbestos is a cause of ovarian cancer, correct?</p> <p>24 A Yes.</p> <p>25 Q Those are References 71 and 72, right?</p>
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<p>1 expert work for plaintiff lawyers in talcum powder</p> <p>2 litigation, correct?</p> <p>3 MS. PARFITT: Objection; form.</p> <p>4 THE WITNESS: Correct.</p> <p>5 Q (By Mr. Williams) Do you know-- do you think the chain</p> <p>6 of custody is important when it comes to samples that are</p> <p>7 being tested for asbestos?</p> <p>8 Do you know what I mean when I say "chain of</p> <p>9 custody"?</p> <p>10 A Why don't you explain it.</p> <p>11 Q Sure.</p> <p>12 I will ask you to assume that "chain of custody"</p> <p>13 refers to who has custody of a particular substance or</p> <p>14 item that is going to be tested from the time that it</p> <p>15 existed at its source to the time that it is tested.</p> <p>16 Do you understand what I mean?</p> <p>17 A Yes.</p> <p>18 Q Do you know where Dr. Longo got the samples that he</p> <p>19 tested?</p> <p>20 A I understood from the summaries in the beginnings of</p> <p>21 these reports that he received the samples from Johnson &amp;</p> <p>22 Johnson.</p> <p>23 Q All of the samples?</p> <p>24 A I would have to look at the individual reports to</p> <p>25 determine that.</p>	<p>1 A Yes.</p> <p>2 Q You also cite Ferrante, F-E-R-R-A-N-T-E, a 2017 pooled</p> <p>3 analysis, in support of your opinion that asbestos is a</p> <p>4 cause of ovarian cancer, right?</p> <p>5 A Yes.</p> <p>6 Q You also cite to the IARC 2012 monograph on asbestos, an</p> <p>7 article by members of the IARC working group, correct?</p> <p>8 A Yes.</p> <p>9 Q Other than those materials, are you relying on anything</p> <p>10 else to support your opinion that asbestos is a cause of</p> <p>11 ovarian cancer?</p> <p>12 A No, I don't believe so, and I did not do a full</p> <p>13 systematic search with causal analysis for asbestos.</p> <p>14 I only did that for talcum powder products.</p> <p>15 Q Why didn't you do one for asbestos?</p> <p>16 A I wasn't asked to.</p> <p>17 Q Were you asked to include a discussion of asbestos in</p> <p>18 your report at all-- excuse me--</p> <p>19 A I was asked to respond about mechanisms-- sorry, to talk</p> <p>20 about mechanisms that may be explaining the association</p> <p>21 between talcum powder products and ovarian cancer risk,</p> <p>22 and when I looked at mechanisms, I often would see the</p> <p>23 potential for asbestos being included in talcum powder</p> <p>24 products, so I wanted to include that as one possible</p> <p>25 mechanism, especially given that asbestos is a known</p>

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<p>1 carcinogen.</p> <p>2 Q Let me focus your attention on Page 57 of your report,</p> <p>3 Exhibit No. 2, to the last sentence in that fourth</p> <p>4 paragraph that says, "IARC concluded that asbestos,</p> <p>5 fibrous talc, chromium, and nickel are Group 1 human</p> <p>6 carcinogens. IARC also classified cobalt as a 2B</p> <p>7 'possible' carcinogen."</p> <p>8 Do you see that?</p> <p>9 A Yes.</p> <p>10 Q Do you believe that Johnson's Baby Powder products</p> <p>11 contained chromium, nickel, and cobalt?</p> <p>12 A I would have to review some of these documents that</p> <p>13 talked about these--</p> <p>14 Q What are you relying on?</p> <p>15 MS. PARFITT: Please let her finish</p> <p>16 the answer.</p> <p>17 MR. WILLIAMS: I'm sorry.</p> <p>18 THE WITNESS: I would need to review</p> <p>19 the documents in the report responding to that.</p> <p>20 Q (By Mr. Williams) Are those heavy metals, the three</p> <p>21 metals I mentioned, the metals that you believe are or</p> <p>22 have ever been present in Johnson's Baby Powder products?</p> <p>23 MS. PARFITT: Objection; form.</p> <p>24 THE WITNESS: Again, I would have to</p> <p>25 review the documents.</p>	<p>1 you have evidence, do you believe that Johnson's Baby</p> <p>2 Powder in particular contains chromium, nickel, and</p> <p>3 cobalt?</p> <p>4 MS. PARFITT: Objection.</p> <p>5 THE WITNESS: I don't have evidence</p> <p>6 one way or the other.</p> <p>7 I did not look at that.</p> <p>8 I looked only at the general comments that talcum</p> <p>9 powder products could contain these metals.</p> <p>10 I did not look at Johnson &amp; Johnson.</p> <p>11 Q (By Mr. Williams) Thank you.</p> <p>12 Are any of your opinions dependent on the assumption</p> <p>13 that the chemicals in the fragrance that goes into</p> <p>14 Johnson's Baby Powder products are carcinogenic?</p> <p>15 A I read one review by Dr. Crowley (Phonetic) who indicated</p> <p>16 that there were quite a few fragrances in these products</p> <p>17 that fall into the classification of carcinogenicity.</p> <p>18 Without that data, my opinion would still stand.</p> <p>19 Q Dr. Crowley is another expert Plaintiffs' witness that</p> <p>20 Plaintiffs' counsel has paid in connection with talc</p> <p>21 litigation, correct?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 THE WITNESS: To my knowledge, yes.</p> <p>24 Q (By Mr. Williams) Have you ever met or spoken with</p> <p>25 Dr. Crowley?</p>
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<p>1 Q (By Mr. Williams) As you sit here today, you are not</p> <p>2 able to tell us what the heavy metals are that are</p> <p>3 supposedly contained in Johnson's Baby Powder?</p> <p>4 MS. PARFITT: Objection; misstates her</p> <p>5 testimony, form.</p> <p>6 THE WITNESS: I would want to review</p> <p>7 the documents.</p> <p>8 Q (By Mr. Williams) Let me ask you this:</p> <p>9 Is it your opinion today, Doctor, that Johnson's</p> <p>10 Baby Powder products contain chromium, nickel, and</p> <p>11 cobalt?</p> <p>12 A Again, I would need to look at the documents to see what</p> <p>13 was found.</p> <p>14 Q So you can't state whether you have that opinion or not?</p> <p>15 MS. PARFITT: Objection. She needs to</p> <p>16 look at the document.</p> <p>17 What documents do you need to see?</p> <p>18 THE WITNESS: I would want to see-- I</p> <p>19 guess Longo-- whoever was looking at these to see what</p> <p>20 was there, but my paragraph did not talk about Johnson &amp;</p> <p>21 Johnson.</p> <p>22 My paragraph talked about talcum powder products</p> <p>23 having these constituents.</p> <p>24 Q (By Mr. Williams) That's my point.</p> <p>25 So as you sit here today, based on your review, do</p>	<p>1 A No, I have not.</p> <p>2 Q Are you relying on Dr. Crowley's litigation report for</p> <p>3 your opinion that perineal use of Johnson's Baby Powder</p> <p>4 products can cause ovarian cancer?</p> <p>5 A Yes, I have looked at his report.</p> <p>6 Q What chemicals did Dr. Crowley identify as fragrance</p> <p>7 constituents contained in Johnson's Baby Powder products?</p> <p>8 A There were many.</p> <p>9 I would have to see the report.</p> <p>10 Do you have it?</p> <p>11 Q I don't want to take the time to do that.</p> <p>12 Let me just ask you this:</p> <p>13 Did you do anything to independently verify whether</p> <p>14 those constituents are, in fact, contained in Johnson's</p> <p>15 Baby Powder products?</p> <p>16 A No, I did not.</p> <p>17 Q We have talked a little bit about IARC today, and I want</p> <p>18 to ask you some questions about that.</p> <p>19 You are familiar with the International Agency for</p> <p>20 Research on Cancer, right?</p> <p>21 A Yes, I am.</p> <p>22 Q You have done work with them?</p> <p>23 A Yes.</p> <p>24 Q IARC has five different categories it places substances</p> <p>25 into with respect to whether they are or may be</p>

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<p>1 carcinogenic, correct?</p> <p>2 A I can't respond to whether it's exactly five or not.</p> <p>3 I have looked at these-- do we have a list of them?</p> <p>4 Q Sure.</p> <p>5 It is-- we'll mark it as Exhibit No. 21.</p> <p>6 (Exhibit No. 21 marked</p> <p>7 for identification.)</p> <p>8</p> <p>9 Q (By Mr. Williams) This is the IARC monograph on talc.</p> <p>10 A 2012?</p> <p>11 Q This one is 2010.</p> <p>12 A 2010, okay.</p> <p>13 Q Let me refer you to Page 35 of the document.</p> <p>14 Do you see "Group 2B" listed there?</p> <p>15 A Yes.</p> <p>16 Q That is where the agent is possibly carcinogenic to</p> <p>17 humans, and then there is a fairly long description of</p> <p>18 what that means.</p> <p>19 Do you see that?</p> <p>20 A Yes.</p> <p>21 Q And it is your understanding that talc has been listed as</p> <p>22 a Group 2B substance?</p> <p>23 A Yes.</p> <p>24 You are using data up to 2006, yes.</p> <p>25 Q Of the almost 1000 substances that IARC has reviewed, do</p>	<p>1 review.</p> <p>2 Q Okay. And let me refer you to Page 35 again, under Group</p> <p>3 2B where that's the definition of the agent being</p> <p>4 possibly carcinogenic to humans.</p> <p>5 Do you see that?</p> <p>6 A Yes.</p> <p>7 Q It says, "This category is used for agents for which</p> <p>8 there is limited evidence of carcinogenicity in humans</p> <p>9 and less than sufficient evidence of carcinogenicity in</p> <p>10 experimental animals."</p> <p>11 Did I read that right?</p> <p>12 A Yes.</p> <p>13 Q Do you remember, as you sit there, the definition of</p> <p>14 "limited evidence of carcinogenicity" under IARC's</p> <p>15 definitions?</p> <p>16 A No, I don't.</p> <p>17 Q Take a look at Page 31.</p> <p>18 On Page 31 of Exhibit No. 21, there is a definition</p> <p>19 at the bottom of the page for "limited evidence of</p> <p>20 carcinogenicity," right?</p> <p>21 A Yes.</p> <p>22 Q And it says, "A positive association has been observed</p> <p>23 between exposure to the agent and cancer for which a</p> <p>24 causal interpretation is considered by the working group</p> <p>25 to be credible, but chance, bias, or confounding could</p>
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<p>1 you know how many have been classified as Group 4, which</p> <p>2 is on the next page, "The agent is probably not</p> <p>3 carcinogenic to humans"?</p> <p>4 A No, I haven't.</p> <p>5 Q If I were to represent to you that there was one, and</p> <p>6 only one, substance that they have reviewed that was put</p> <p>7 into Group 4, would that surprise you?</p> <p>8 MS. PARFITT: Objection; form.</p> <p>9 THE WITNESS: It would not surprise me</p> <p>10 because they probably are only looking at things that are</p> <p>11 potentially carcinogenic.</p> <p>12 Q (By Mr. Williams) You mentioned earlier today that IARC</p> <p>13 sets a high bar for listing something as a Group 2B</p> <p>14 possible substance.</p> <p>15 Do you remember saying that?</p> <p>16 A I don't, but I believe you.</p> <p>17 Q What was the basis for your statement that IARC sets a</p> <p>18 high bar as opposed to some other level bar for</p> <p>19 determining whether a substance is a Group 2B substance?</p> <p>20 A From my understanding, they do a systematic review. They</p> <p>21 set up a panel of scientists, and then they do a</p> <p>22 systematic review, including studies from humans and</p> <p>23 animals, and they did this for-- for talcum powder</p> <p>24 products-- for talc, they did it up to 2006, and they did</p> <p>25 not do meta-analysis, but they did do a systematic</p>	<p>1 not be ruled out with reasonable confidence."</p> <p>2 Did I read that right?</p> <p>3 A Yes.</p> <p>4 Q Remember earlier today we were talking about chance,</p> <p>5 bias, and confounding factors needing to be ruled out in</p> <p>6 order to move something from a Group 2B designation to a</p> <p>7 higher designation, and you said, "I would have to look</p> <p>8 at the IARC monograph"?</p> <p>9 Do you remember that?</p> <p>10 A Yes.</p> <p>11 Q Now that we are looking at the IARC monograph, and you</p> <p>12 see the definition of "limited evidence of</p> <p>13 carcinogenicity," will you agree with me now that in</p> <p>14 order for something to move up from this Level 2B, where</p> <p>15 there's limited evidence of carcinogenicity in humans, to</p> <p>16 some higher level, one would need to rule out or</p> <p>17 specifically the IARC group would need to rule out</p> <p>18 chance, bias, and confounding?</p> <p>19 MS. PARFITT: Objection; form.</p> <p>20 THE WITNESS: Yes, because they state</p> <p>21 that in the category above, "Sufficient."</p> <p>22 Q (By Mr. Williams) And when you say "yes," "yes," they</p> <p>23 would have to rule out all of those things, correct?</p> <p>24 A Yes, with reasonable confidence.</p> <p>25 Q Now, as we sit here today, IARC still lists talc as a 2B</p>



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<p>1 substance, correct?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: IARC has not updated</p> <p>4 their 2006 data, correct.</p> <p>5 Q (By Mr. Williams) Therefore the most recent update lists</p> <p>6 talc as a Group 2B substance, correct?</p> <p>7 MS. PARFITT: Objection; form.</p> <p>8 THE WITNESS: Using data up to 2006,</p> <p>9 yes.</p> <p>10 Q (By Mr. Williams) You keep saying, "using data up to</p> <p>11 2006."</p> <p>12 Do you have any basis for-- strike that.</p> <p>13 You testified earlier today that you believe that</p> <p>14 IARC would set a higher designation if they had the</p> <p>15 results of studies since 2006, correct?</p> <p>16 A I believe it would be reasonable to expect that, given</p> <p>17 that there's more studies published since that time.</p> <p>18 Q And when you say that you believe it would be reasonable</p> <p>19 to expect that, you expected it, right?</p> <p>20 MS. PARFITT: Objection.</p> <p>21 THE WITNESS: I can't say what a panel</p> <p>22 of scientists would say if it was faced with reviewing</p> <p>23 the literature.</p> <p>24 All I can say is the literature-- all I can say is</p> <p>25 the literature has been increased significantly in the</p>	<p>1 you relied upon in preparing your report, correct?</p> <p>2 A Yes.</p> <p>3 Q It was published in 2008?</p> <p>4 A Yes.</p> <p>5 Q That is two years after IARC met to discuss talc?</p> <p>6 A Yes.</p> <p>7 Q Three of the four authors of this meta-analysis were</p> <p>8 participants in the IARC working group.</p> <p>9 Do you remember that?</p> <p>10 A Yes.</p> <p>11 Q If you look at the last page of this exhibit, Exhibit</p> <p>12 No. 22, there's an acknowledgments section on Page 360.</p> <p>13 It says, "The work reported in this paper was</p> <p>14 initiated while SH, JS, and EW were part of an IARC</p> <p>15 monograph working group of the International Agency for</p> <p>16 Research on Cancer, Lyon, France."</p> <p>17 Do you see that?</p> <p>18 A Yes.</p> <p>19 Q So after the working group determined, and by that I mean</p> <p>20 the IARC working group determined, that chance, bias, or</p> <p>21 confounding could not be ruled out as an explanation for</p> <p>22 the reported association between talc and ovarian cancer,</p> <p>23 three of the members of that working group continued</p> <p>24 their work in this article, correct?</p> <p>25 MS. PARFITT: Objection; form,</p>
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<p>1 last ten years.</p> <p>2 Q (By Mr. Williams) And what study are you referring to or</p> <p>3 studies are you referring to?</p> <p>4 A So some of the larger case-control studies that were</p> <p>5 published in recent years, the two meta-analyses, and the</p> <p>6 pooled analysis.</p> <p>7 Q Anything else?</p> <p>8 A In terms of epidemiology, that's it.</p> <p>9 Q Let me show you to one of the studies that has been done</p> <p>10 since the IARC monograph was first drafted in 2006.</p> <p>11 We'll mark it as Exhibit No. 22.</p> <p>12 (Exhibit No. 22 marked</p> <p>13 for identification.)</p> <p>14</p> <p>15 Q (By Mr. Williams) The Langseth study, which is Exhibit</p> <p>16 No. 22, is one of the studies there you rely upon,</p> <p>17 correct?</p> <p>18 A That's correct.</p> <p>19 Q Let me ask you to turn to Page 360, which is the-- I</p> <p>20 believe the last page of the study.</p> <p>21 Do you see that there are 34 publications cited as</p> <p>22 references to the Langseth article?</p> <p>23 A Yes.</p> <p>24 Q For the record, "Langseth" is L-A-N-G-S-E-T-H.</p> <p>25 The Langseth study was one of the meta-analyses that</p>	<p>1 misstates the substance of this article.</p> <p>2 THE WITNESS: Yes.</p> <p>3 Q (By Mr. Williams) You may answer.</p> <p>4 A Yes.</p> <p>5 Q Does this paper report the perineal use of talc in fact</p> <p>6 causes ovarian cancer?</p> <p>7 A I don't see that they did a full causal analysis in this</p> <p>8 paper, but I see that they have a pooled odds ratio of</p> <p>9 1.35, which is statistically significant.</p> <p>10 Yeah, 1.35.</p> <p>11 Q You read this study, right?</p> <p>12 A Yes.</p> <p>13 Q Let's take a look at Page 359.</p> <p>14 Under the heading "Proposal to research community,"</p> <p>15 do you see that?</p> <p>16 A Yes.</p> <p>17 Q Right underneath that it says, "The current body of</p> <p>18 experimental and epidemiological evidence is insufficient</p> <p>19 to establish a causal association between perineal use of</p> <p>20 talc and ovarian cancer risk."</p> <p>21 Did I read that right?</p> <p>22 A Yes.</p> <p>23 Q Can you and I agree that that is the opposite of the</p> <p>24 conclusion that you are intending to express in this</p> <p>25 litigation?</p>

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<p>1 MS. PARFITT: Objection; form.</p> <p>2 THE WITNESS: Using information</p> <p>3 available to 2018, I do have a different opinion than</p> <p>4 these investigators did in using their data up to 2006.</p> <p>5 Q (By Mr. Williams) They-- strike that.</p> <p>6 They would have information up until the time they</p> <p>7 published this study, the Langseth study, right, which</p> <p>8 was done in 2008?</p> <p>9 MS. PARFITT: Objection.</p> <p>10 THE WITNESS: Not necessarily up until</p> <p>11 this date.</p> <p>12 It takes a while to get-- it was accepted in 2007,</p> <p>13 so their data are going to be studies probably only up to</p> <p>14 2006, if the paper was already written and accepted in</p> <p>15 2007, October.</p> <p>16 Q (By Mr. Williams) After this Langseth paper was</p> <p>17 published, there were large cohort studies, prospective</p> <p>18 studies, that were published, true?</p> <p>19 A They were small in terms of the number of cases.</p> <p>20 They came from large cohorts, but the number of</p> <p>21 cases were small.</p> <p>22 Q Are you referring to the cohort studies that were</p> <p>23 published in 2008, 2010, and 2014?</p> <p>24 MS. PARFITT: Objection; form.</p> <p>25 THE WITNESS: Two thousand-- yes-- how</p>	<p>1 combined?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: I don't think we had-- I</p> <p>4 don't think we discussed that particular-- and we didn't</p> <p>5 do a power analysis with the numbers that they had, but</p> <p>6 together they had-- what was it, 900, so they probably</p> <p>7 were powered with a relative risk of 1.3.</p> <p>8 Q (By Mr. Williams) Well, whatever that testimony was, it</p> <p>9 was.</p> <p>10 Let me ask you this:</p> <p>11 It is a fact that after the IARC monograph-- strike</p> <p>12 that.</p> <p>13 After-- it is a fact that after the data that</p> <p>14 underlay the IARC monograph, after the Langseth study was</p> <p>15 published in 2008, there were additional cohort studies</p> <p>16 that were published, correct?</p> <p>17 A As well as about eight case-control studies.</p> <p>18 Quite a few studies were published after.</p> <p>19 Q And based upon that, you speculate that if IARC were to</p> <p>20 undertake an analysis of whether talc is causally</p> <p>21 associated with ovarian cancer, that you believe that</p> <p>22 they would change their mind?</p> <p>23 MS. PARFITT: Objection; form.</p> <p>24 THE WITNESS: I speculate it would be</p> <p>25 reasonable for a scientific panel to come up with a</p>
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<p>1 many cases do we have?</p> <p>2 I think we covered that earlier, the number of cases</p> <p>3 that would be needed.</p> <p>4 So Women's Health Initiative published in 2014 had</p> <p>5 429 cases.</p> <p>6 The sister study in 2016 had 154.</p> <p>7 The Nurses' Health Study, which the problem with</p> <p>8 that was they weren't-- they changed their categories</p> <p>9 with exposure, but that one did have a larger number,</p> <p>10 797.</p> <p>11 Q (By Mr. Williams) You remember earlier today we went</p> <p>12 through the whole discussion of whether or not there were</p> <p>13 sufficient number of cases, right?</p> <p>14 A And that was a different discussion that was about the</p> <p>15 pooled analysis-- sorry, the meta-analysis of the cohort</p> <p>16 studies.</p> <p>17 It wasn't about these individual studies.</p> <p>18 Q Let me talk to you now about the meta-analysis of those</p> <p>19 studies that were conducted that are cohort studies.</p> <p>20 Do you have those in mind?</p> <p>21 A Yes.</p> <p>22 Q Do you wish to change any of the testimony that you gave</p> <p>23 earlier today concerning the-- whether or not there was a</p> <p>24 sufficient number of cases, as part of the pooled</p> <p>25 analysis, for the cohort studies to have power if</p>	<p>1 different classification after reviewing the new human</p> <p>2 data that have been available the last ten years.</p> <p>3 MR. WILLIAMS: Let's take one final</p> <p>4 break, if we can.</p> <p>5 VIDEOGRAPHER: Going off the record,</p> <p>6 the time is 4:54 p.m.</p> <p>7 (Recess 4:54 to 5:09 p.m.)</p> <p>8</p> <p>9 VIDEOGRAPHER: We are back on the</p> <p>10 record. The time is 5:09 p.m.</p> <p>11 Q (By Mr. Williams) Dr. McTiernan, just a few more minutes</p> <p>12 from me, and then we have just a couple minutes of</p> <p>13 questioning from Imerys counsel, but I have to do it. I</p> <p>14 have to have you grab the Berge study one more time,</p> <p>15 Exhibit No. 16A.</p> <p>16 Earlier today, this afternoon actually, we had a</p> <p>17 discussion about statistical significance, and I was</p> <p>18 trying to focus you on statistical significance as it</p> <p>19 relates to the cohort studies that are listed on page--</p> <p>20 listed in Figure No. 2 on Page 7 of Exhibit No. 16A.</p> <p>21 Do you have that in front of you?</p> <p>22 A Yes.</p> <p>23 Q And you'll recall that I focused you on the subtotal for</p> <p>24 cohort studies with regard to what the relative risk was</p> <p>25 and the confidence interval, and you noted that it was</p>

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<p>1 1.02 as a relative risk with a confidence interval that</p> <p>2 goes all the way up to 1.20.</p> <p>3 Do you recall that?</p> <p>4 A Yes.</p> <p>5 Q And when I made the point that it was lacking statistical</p> <p>6 significance, you said, "But the confidence interval</p> <p>7 includes one, so that would not be statistically</p> <p>8 significant, but it ranges up to 1.2, which means that</p> <p>9 the relative risk could be as high as 1.2 for the cohort</p> <p>10 study."</p> <p>11 Do you recall saying that?</p> <p>12 A Correct.</p> <p>13 Q It is equally true, based on the confidence interval</p> <p>14 reported on Page 7, that the relative risks could be as</p> <p>15 low as 0.85, correct?</p> <p>16 A That's correct.</p> <p>17 Q And with respect to each of the case-control studies that</p> <p>18 did not find statistical significance, first you see</p> <p>19 Cramer in 1982, that one that had a 0.70 relative risk--</p> <p>20 you see that one?</p> <p>21 A Yes.</p> <p>22 Q That one had a low--</p> <p>23 A That's Hartge.</p> <p>24 Q That's Hartge, pardon me. I shouldn't have said</p> <p>25 "Cramer."</p>	<p>1 of the confidence interval was 0.70, correct?</p> <p>2 A Yes.</p> <p>3 One thing that all of these studies had in common is</p> <p>4 they were very small, and you get a very wide confidence</p> <p>5 interval with these small studies.</p> <p>6 You notice the larger studies, the confidence</p> <p>7 intervals, such as Cramer 2016, was 1.14 up to 1.5.</p> <p>8 That's a much more narrow confidence interval, and that's</p> <p>9 because it's a larger study.</p> <p>10 Q So let's focus now on what we were focused on this</p> <p>11 afternoon, which is the cohort studies.</p> <p>12 With respect to the cohort studies, in the aggregate</p> <p>13 the low point was 0.85, correct?</p> <p>14 A That's correct.</p> <p>15 Q And those cohort studies, we established earlier today,</p> <p>16 have a total number of cases that exceeded 1300, right?</p> <p>17 A Correct.</p> <p>18 Q That's all I need on that.</p> <p>19 I wanted to ask you about one of the Bradford Hill</p> <p>20 elements or factors, the one that has to do with</p> <p>21 biological plausibility, okay?</p> <p>22 A Mm-hm.</p> <p>23 Q Is that a "yes"?</p> <p>24 A Yes.</p> <p>25 Q Okay. So can you cite a single study, animal or human,</p>
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<p>1 Let me start again.</p> <p>2 The first case-control study that did not have a</p> <p>3 statistically significant relative risk was Hartge 1983,</p> <p>4 right?</p> <p>5 A Yes.</p> <p>6 Q And its lower confidence interval, the low side of that,</p> <p>7 was 0.83, correct?</p> <p>8 A You're looking at Whittemore, but I think you're talking</p> <p>9 about Hartge.</p> <p>10 Q Sorry, 0.40.</p> <p>11 A Yes.</p> <p>12 Q So the relative risk for Hartge could go as low as 0.40,</p> <p>13 right?</p> <p>14 A Yes.</p> <p>15 Q The relative risk for Whittemore could go as low as 0.83,</p> <p>16 right?</p> <p>17 A Yes.</p> <p>18 What it means is a 95 percent chance that the risk</p> <p>19 is within that range, 0.83 up to 1.74.</p> <p>20 Q So it could be as high as 1.74 for Whittemore or as low</p> <p>21 as 0.83?</p> <p>22 A That's correct.</p> <p>23 Q And for Booth, the low point was 0.80, correct?</p> <p>24 A Yes.</p> <p>25 Q And for the next one, Harlow &amp; Weiss, 1989, the low end</p>	<p>1 that traces externally applied talc up through the</p> <p>2 reproductive organs to the ovaries?</p> <p>3 MS. PARFITT: Objection; form.</p> <p>4 THE WITNESS: So the question is</p> <p>5 externally applied talc?</p> <p>6 MR. WILLIAMS: Correct.</p> <p>7 THE WITNESS: So in humans that would</p> <p>8 be unethical to do to see if that can move up to the</p> <p>9 ovaries.</p> <p>10 In terms of animals-- so in animals, talc was placed</p> <p>11 in the vaginas, and it moved within four days up to the</p> <p>12 ovaries.</p> <p>13 Q (By Mr. Williams) And which study is that?</p> <p>14 A That's on Henderson 86.</p> <p>15 Q Okay. Thank you.</p> <p>16 Anything else?</p> <p>17 A Let me see.</p> <p>18 In terms of humans, quite a few have been done with</p> <p>19 particles of similar size to talc, which was thought to</p> <p>20 be-- let me try to find where I have these.</p> <p>21 So it wouldn't have the ethical issue, so inert</p> <p>22 particles of carbon black were placed in women's vaginas</p> <p>23 and were found to move in 30 minutes in two of three</p> <p>24 patients, and that's the Egli study.</p> <p>25 Q Which one is that?</p>

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<p>1 A Egli, E-G-L-I.</p> <p>2 Q Anything else?</p> <p>3 A There was a surgical glove study with starch.</p> <p>4 There was one radioactive tracer labelled human</p> <p>5 albumin microspheres placed in-- there was--</p> <p>6 radio-labelled albumin was placed in women's vaginas one</p> <p>7 day before pelvic surgery, and of 14 women, nine showed</p> <p>8 radioactivity in the fallopian tubes.</p> <p>9 Q Which study was that?</p> <p>10 A So that was the Venter, V-E-N-T-E-R.</p> <p>11 One study on migration of talc-- sorry, no,</p> <p>12 evaluated powder, so this was a starch powder on surgical</p> <p>13 gloves that were used to perform pelvic exam in advance</p> <p>14 of surgery, and they found statistically significant-- so</p> <p>15 this is the Sjosten study. It's S-J-O-S-T-E-N.</p> <p>16 Q Anything else?</p> <p>17 A And that's in terms of migration for humans and animals,</p> <p>18 I believe.</p> <p>19 Q So is it accurate to say that not one of the studies that</p> <p>20 you just mentioned -- Egli, Venter, Sjosten or Henderson</p> <p>21 -- involves tracing externally applied talc in the</p> <p>22 perineal area up through the reproductive organs through</p> <p>23 the ovaries?</p> <p>24 A There are no such studies in humans, that's correct.</p> <p>25 It would be unethical to apply it externally and</p>	<p>1 Q But none of the studies that you mentioned involve</p> <p>2 reviewing perineal use external to the vagina and</p> <p>3 followed the talc up through the reproductive organs,</p> <p>4 true or not true?</p> <p>5 A That's correct.</p> <p>6 Q Can you cite any published study concluding that</p> <p>7 particles on the outside of the vagina can migrate inside</p> <p>8 and up the genital tract to the ovary?</p> <p>9 A I don't believe it was cited in my report.</p> <p>10 Q Assuming for a moment that talcum powder can reach the</p> <p>11 ovaries, is it your opinion that talcum powder produces</p> <p>12 chronic inflammation that somehow leads to ovarian</p> <p>13 cancer?</p> <p>14 A Yes, it is my opinion that it can cause chronic</p> <p>15 inflammation and it doesn't need to reach the ovaries.</p> <p>16 Many cancers, especially serous cancers, are thought</p> <p>17 to begin in the fallopian tubes, and they would need to</p> <p>18 rise as high as that.</p> <p>19 Q So inflammation is the biological mechanism that you</p> <p>20 believe is plausible for perineal talc use to cause</p> <p>21 ovarian cancer, correct?</p> <p>22 A I believe it's one very plausible mechanism.</p> <p>23 Q There are no reports in the literature of externally</p> <p>24 applied talcum powder products leading to inflammation,</p> <p>25 granulomas, fibrosis, or adhesions anywhere along a</p>
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<p>1 follow it up through the pelvic organs.</p> <p>2 Q Same with the animals though, none of the animal studies</p> <p>3 that you just mentioned, or the only animal study you</p> <p>4 mentioned, does not deal with externally applied talc</p> <p>5 moving up through the reproductive organs through the</p> <p>6 ovaries, correct?</p> <p>7 MS. PARFITT: Object to form.</p> <p>8 THE WITNESS: They're vaginally</p> <p>9 applied.</p> <p>10 Q (By Mr. Williams) In the vagina, correct?</p> <p>11 A Into the vagina, yes.</p> <p>12 Q So you and I can agree that there is a difference between</p> <p>13 the outer area and inside the vagina?</p> <p>14 MS. PARFITT: Objection.</p> <p>15 THE WITNESS: There are plenty of ways</p> <p>16 for which anything on the external part of the peroneum</p> <p>17 can move into the vagina.</p> <p>18 Q (By Mr. Williams) There's not one study that you've</p> <p>19 cited for humans that involved particles other than talc</p> <p>20 or any known toxic substance.</p> <p>21 There are articles that inject into the vagina the</p> <p>22 particles and they see what happens, right?</p> <p>23 A Mm-hm.</p> <p>24 Q Is that "yes"?</p> <p>25 A Yes.</p>	<p>1 woman's reproductive tract, correct?</p> <p>2 MS. PARFITT: Objection; form.</p> <p>3 THE WITNESS: Again, it's the ethics</p> <p>4 of applying something that could potentially be</p> <p>5 carcinogenic to see what would occur.</p> <p>6 Q (By Mr. Williams) Can you identify any study that shows</p> <p>7 inflammation, granulomas, fibrosis, or adhesions anywhere</p> <p>8 along a woman's reproductive tract as a result of her</p> <p>9 external genital talcum powder application?</p> <p>10 A I don't think I cited any such studies.</p> <p>11 Q Can you identify any published animal study where talcum</p> <p>12 powder actually caused ovarian cancer in the animal?</p> <p>13 A There have been studies that showed that talc can lead to</p> <p>14 cyst formation and epithelial changes in rats.</p> <p>15 Q Which study is that?</p> <p>16 A That is 122.</p> <p>17 Hamilton.</p> <p>18 Q Any other studies?</p> <p>19 A Say that again?</p> <p>20 Q You said "Hamilton," right?</p> <p>21 A Hamilton, 1984.</p> <p>22 Q Any other studies?</p> <p>23 A Oh, and a mouse study, which is 123, Van Dyke.</p> <p>24 Q 123?</p> <p>25 A 123, yes, that talc can cause super NI generation and</p>

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<p>1 release from mouth to macrophages (phonetic).</p> <p>2 Q Anything else?</p> <p>3 A I am just looking.</p> <p>4 So you are talking about ovarian tumors.</p> <p>5 The NTP, the National Toxicology Program, has also</p> <p>6 done rat studies and found that exposure to talc cause--</p> <p>7 it was an inhalation study, caused clear evidence of</p> <p>8 carcinogenesis in females in terms of cancer of the</p> <p>9 adrenal gland and the lung and possible carcinogenic</p> <p>10 activity in males.</p> <p>11 Q What was the date of that NTP study?</p> <p>12 A NTP study? That was No. 124.</p> <p>13 1993.</p> <p>14 Q Are you familiar with the methodology of that study?</p> <p>15 A I have read the study, yes.</p> <p>16 Q And you know that the rats were subjected to talcum</p> <p>17 powder pumped into a cage-- a closed cage, I think it</p> <p>18 was, six hours a day, five days a week, for their entire</p> <p>19 lives, right?</p> <p>20 A Yes.</p> <p>21 Q Do you think that that has applicability to human beings</p> <p>22 using talcum powder in their homes?</p> <p>23 MS. PARFITT: Objection; form.</p> <p>24 THE WITNESS: Using talcum powder in--</p> <p>25 Q (By Mr. Williams) In their homes.</p>	<p>1 concluded that the 1993 rat study was not applicable or</p> <p>2 appropriate for application to humans?</p> <p>3 MS. PARFITT: Objection; misstates the</p> <p>4 evidence.</p> <p>5 Q (By Mr. Williams) I'm sorry, I misspoke.</p> <p>6 Are you aware that the FDA concluded that the 1993</p> <p>7 NTP study was not applicable to human beings?</p> <p>8 MS. PARFITT: Objection; misstates the</p> <p>9 evidence in the case.</p> <p>10 THE WITNESS: I would have to see both</p> <p>11 the FDA statement and the NTP.</p> <p>12 Q (By Mr. Williams) Can you identify-- strike that.</p> <p>13 I want to distinguish between a study, an animal</p> <p>14 study, where talcum powder caused inflammation on the one</p> <p>15 hand, with an animal study that found that talcum powder</p> <p>16 caused ovarian cancer.</p> <p>17 Do you have that distinction that I'm making in</p> <p>18 mind?</p> <p>19 Do you have the distinction I'm making in mind?</p> <p>20 A I'm just reading through my report.</p> <p>21 Q Inflammation on the one hand, ovarian cancer on the</p> <p>22 other.</p> <p>23 I am trying to make that distinction.</p> <p>24 Do you have that distinction in mind?</p> <p>25 When you say "yes," I'll ask you a question.</p>
Page 295	Page 297
<p>1 A I think the correlation would be a larger concentrated</p> <p>2 dose being introduced into the genital tract, and if the</p> <p>3 talc is carcinogenic to animals and wasn't seen in the</p> <p>4 control animals, then it's still concerning.</p> <p>5 Q Did the 1993 NTP study in fact report any ovarian cancer</p> <p>6 in the female rats or mice?</p> <p>7 A I don't believe that these rats developed ovarian cancer.</p> <p>8 They did not develop ovarian cancer.</p> <p>9 Q Not one of them did, correct?</p> <p>10 A No.</p> <p>11 It may not be an ovarian cancer model.</p> <p>12 Q Did the 1993 NTP study report any neoplastic changes in</p> <p>13 the ovaries of the female rats or mice?</p> <p>14 A Not to my knowledge.</p> <p>15 Again, it's not a model for ovarian cancer.</p> <p>16 Q Can we agree that the NTP 1993 rat and mouse study does</p> <p>17 not in fact show that talc causes inflammation, which</p> <p>18 inflammation leads to neoplastic change or cancer in an</p> <p>19 animal's ovaries?</p> <p>20 MS. PARFITT: Objection; form.</p> <p>21 THE WITNESS: I don't have the study</p> <p>22 in front of me.</p> <p>23 I don't recall that they did the full mechanistic</p> <p>24 study.</p> <p>25 Q (By Mr. Williams) Do you recall that the NTP expressly</p>	<p>1 A So in Genofre's, G-E-N-O-F-R-E, study, in animal models,</p> <p>2 injection of talc into the pleura causes local and</p> <p>3 systemic inflammatory response, so it includes elevated</p> <p>4 levels of C-reactive protein and interleukin 6, and CEGF</p> <p>5 and TGF beta, and several of these are associated with</p> <p>6 increased risk of ovarian cancer in humans, including</p> <p>7 C-reactive protein and interleukin 8.</p> <p>8 Q Did that study that you are referring to, the Genofre,</p> <p>9 G-E-N-O-F-R-E, 2009 study, are you saying that that study</p> <p>10 showed that talc caused inflammation that led to</p> <p>11 neoplastic or cancerous changes in the animals?</p> <p>12 A This was a model looking at inflammation.</p> <p>13 Q And did that study show that talc application to the</p> <p>14 animal caused inflammation that led to cancerous changes?</p> <p>15 A To my knowledge, it stopped at the inflammatory response.</p> <p>16 Q None of the studies that you are relying upon -- Genofre</p> <p>17 -- compared C-reactive proteins, and that's C hyphen</p> <p>18 reactive proteins, or IL 8 levels between perineal talc</p> <p>19 users and nontalc users, correct?</p> <p>20 MS. PARFITT: Objection; form.</p> <p>21 THE WITNESS: I don't know about</p> <p>22 research that has looked at that.</p> <p>23 I do know that women with high levels of C-reactive</p> <p>24 protein or interleukin 8 are at an increased risk of</p> <p>25 developing ovarian cancer.</p>



<p style="text-align: right;">Page 298</p> <p>1 Q (By Mr. Williams) None of the studies that you rely on</p> <p>2 concluded that C-reactive proteins or IL 8 levels can</p> <p>3 cause a local inflammatory response in the ovary,</p> <p>4 correct?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: C-reactive protein and</p> <p>7 interleukin 8 are the inflammatory response.</p> <p>8 They are the products that are made during</p> <p>9 inflammatory response, to my knowledge.</p> <p>10 Q (By Mr. Williams) Was that an inflammatory response in</p> <p>11 the ovary?</p> <p>12 A It was blood-- the epidemiologic studies you are talking</p> <p>13 about was in blood.</p> <p>14 Q Can you identify any published study concluding that</p> <p>15 increased C-reactive protein levels leads to ovarian</p> <p>16 cancer in humans?</p> <p>17 A Yes, I have that.</p> <p>18 I am looking for it.</p> <p>19 I thought that I had reference to meta-analysis of</p> <p>20 C-reactive protein and risk of ovarian cancer, but it's</p> <p>21 not showing up.</p> <p>22 Q Can you identify any published study concluding that the</p> <p>23 C-reactive protein levels are greater in perineal talc</p> <p>24 users than nonperineal talc users?</p> <p>25 A I did not look at that.</p>	<p style="text-align: right;">Page 300</p> <p>1 Q Okay. That they, for a period of time, supplied the raw</p> <p>2 material talc to Johnson &amp; Johnson for the baby powder.</p> <p>3 Are you aware of that?</p> <p>4 A I was aware that they did supply.</p> <p>5 I don't know anything about when or how much, no.</p> <p>6 Q Okay. So just a couple areas of questions:</p> <p>7 There were some questions that Mr. Williams asked</p> <p>8 you regarding chromium, nickel, and cobalt, and you said</p> <p>9 you do not know if those were contained in the Johnson &amp;</p> <p>10 Johnson powder specifically.</p> <p>11 Do you recall that?</p> <p>12 A I do recall saying that.</p> <p>13 Q Okay. Same question as to Imerys.</p> <p>14 You do not know if Imerys raw talc specifically</p> <p>15 contained chromium, nickel, or cobalt, do you?</p> <p>16 A I would have to look.</p> <p>17 I know that the Pier deposition had some information</p> <p>18 at least about some of the talc.</p> <p>19 Do we have that?</p> <p>20 MS. PARFITT: Give us one moment.</p> <p>21 Do you want to have her identify--</p> <p>22 MS. ERFLE: Please do.</p> <p>23 THE WITNESS: So this is Exhibit</p> <p>24 No. 47 of Pier testimony, 9/13/18.</p> <p>25 Q (By Ms. Erfle) That's great. Let's look at that.</p>
<p style="text-align: right;">Page 299</p> <p>1 Q Can you identify any published study concluding that the</p> <p>2 interleukin, and that's I-N-T-E-R-L-E-U-K-I-N, dash 8</p> <p>3 levels are greater in perineal talc users than</p> <p>4 nonperineal talc users?</p> <p>5 A I did not look at that.</p> <p>6 MR. WILLIAMS: That's all the</p> <p>7 questions I have, Doctor. Thank you very much.</p> <p>8 Let's go off the record.</p> <p>9 VIDEOGRAPHER: Going off the record,</p> <p>10 the time is 5:33 p.m. Please stand by.</p> <p>11 (Recess 5:33 to 5:35 p.m.)</p> <p>12</p> <p>13 VIDEOGRAPHER: We are back on the</p> <p>14 record. The time is 5:35 p.m.</p> <p>15</p> <p>16</p> <p>17 EXAMINATION</p> <p>18 BY MS. ERFLE:</p> <p>19 Q Dr. McTiernan, again, my name is Nancy Erfle. I</p> <p>20 represent Imerys Talc America, and you understand that's</p> <p>21 a different defendant than Johnson &amp; Johnson, correct?</p> <p>22 A Yes, I do.</p> <p>23 Q And do you understand the role in this litigation, what</p> <p>24 their role is?</p> <p>25 A No. You can explain it.</p>	<p style="text-align: right;">Page 301</p> <p>1 So you have that in front of you?</p> <p>2 A Yes.</p> <p>3 Q And what about that indicates that there is chromium,</p> <p>4 nickel, or cobalt in the raw material specifically</p> <p>5 provided to Johnson &amp; Johnson?</p> <p>6 A So these samples are all from Imerys--</p> <p>7 Q Do you know that to be the case?</p> <p>8 A That was my understanding, that that was the case, and I</p> <p>9 see Exhibit No. 38, chromium, cobalt, and nickel in a</p> <p>10 Johnson &amp; Johnson sample.</p> <p>11 Q Okay. Do you know-- can you say-- how do you know that</p> <p>12 that's a J&amp;J sample?</p> <p>13 A This is what is stated by the expert witness, to my</p> <p>14 understanding.</p> <p>15 Q So you've done no independent work yourself to confirm</p> <p>16 what these are or what these samples are, correct?</p> <p>17 A That's correct.</p> <p>18 I am relying on this testimony.</p> <p>19 Q So you don't know if these were actually samples that</p> <p>20 went into a Johnson &amp; Johnson bottle that reached a</p> <p>21 consumer, correct?</p> <p>22 MS. PARFITT: Objection; form.</p> <p>23 Q (By Ms. Erfle) You can answer.</p> <p>24 A Correct.</p> <p>25 Q And you don't know if any of these items listed in</p>

<p style="text-align: right;">Page 302</p> <p>1 Exhibit No. 47 of Ms. Pier's exhibit-- Exhibit No. 47</p> <p>2 from Ms. Pier's prior testimony, if any of that actually</p> <p>3 went to a competitor or was a competitor's product not</p> <p>4 Imerys, correct?</p> <p>5 MS. PARFITT: Objection; form.</p> <p>6 THE WITNESS: Correct, I don't know</p> <p>7 from this data.</p> <p>8 Q (By Ms. Erfle) And you don't know from Exhibit No. 47</p> <p>9 from Ms. Pier's prior deposition, that you are looking at</p> <p>10 now, if any of that talc came from mines that were never</p> <p>11 actually used for Johnson &amp; Johnson product, correct?</p> <p>12 MS. PARFITT: Objection; form.</p> <p>13 THE WITNESS: Well, this does state</p> <p>14 "Johnson &amp; Johnson company" on two of the samples that</p> <p>15 have chromium, cobalt, and nickel.</p> <p>16 Q (By Ms. Erfle) But, again, you don't know if that</p> <p>17 actually ever reached into a product that became body</p> <p>18 powder from Johnson &amp; Johnson that went to a consumer,</p> <p>19 correct?</p> <p>20 MS. PARFITT: Objection; form.</p> <p>21 THE WITNESS: Correct.</p> <p>22 (Exhibit No. 23 marked</p> <p>23 for identification.)</p> <p>24 Q (By Ms. Erfle) And just to make the record clear, let's</p> <p>25 put in as Exhibit No. 23 the Julie Pier document that you</p>	<p style="text-align: right;">Page 304</p> <p>1 A It should be, yes.</p> <p>2 (Exhibit No. 25 marked</p> <p>3 for identification.)</p> <p>4</p> <p>5 Q (By Ms. Erfle) Let's mark as Exhibit No. 25 this-- can</p> <p>6 you identify that for the record?</p> <p>7 A This is a copy of my report with notes on it.</p> <p>8 Yeah, it's a copy of my report, expert report, of</p> <p>9 November 16th, 2018.</p> <p>10 Q And it's the one with your handwritten notes?</p> <p>11 A Yes.</p> <p>12 Q Okay. One last question:</p> <p>13 Do you have an invoice that you've generated from</p> <p>14 December of 2018 through today, which is January 28th,</p> <p>15 2019?</p> <p>16 A Not yet.</p> <p>17 Q Okay. And once you generate that invoice, will you</p> <p>18 please give it to your counsel and make sure that they</p> <p>19 provide it to us?</p> <p>20 A Mm-hm.</p> <p>21 Q Is that a "yes"?</p> <p>22 A Yes. Yes.</p> <p>23 MS. ERFLE: Okay. That's all I have.</p> <p>24 MR. GOLOMB: How much time do you have</p> <p>25 left--</p>
<p style="text-align: right;">Page 303</p> <p>1 are looking at, so we make sure it's a little clearer.</p> <p>2 So all the questions I just asked you,</p> <p>3 Dr. McTiernan, about the Julie Pier Exhibit No. 47, it's</p> <p>4 also the same document as we've marked as Exhibit No. 23</p> <p>5 to your deposition, correct?</p> <p>6 A I can't read the whole thing, but it looks the same--</p> <p>7 it's the same number.</p> <p>8 Q I will represent to you that that's another copy of it,</p> <p>9 but it's marked as Exhibit No. 23 to this deposition,</p> <p>10 okay?</p> <p>11 A Okay.</p> <p>12 Q Are you okay with that?</p> <p>13 A Yes.</p> <p>14 (Exhibit No. 24 marked</p> <p>15 for identification.)</p> <p>16</p> <p>17 Q (By Ms. Erfle) Last thing I want to do is put in as</p> <p>18 Exhibit No. 24-- Dr. McTiernan, can you please look at</p> <p>19 that and identify that for the record, Exhibit No. 24?</p> <p>20 A These are invoices that I submitted to Ms. Parfitt's firm</p> <p>21 for work up until December 2018.</p> <p>22 Q Okay. So let's mark as Exhibit No.-- and are those a</p> <p>23 complete copy of all invoices that you would have</p> <p>24 incurred from the time you began your work on this</p> <p>25 litigation up until December of 2018?</p>	<p style="text-align: right;">Page 305</p> <p>1 MR. LOCKE: I don't think there's any</p> <p>2 more time.</p> <p>3 MR. GOLOMB: How much time is there on</p> <p>4 that disc?</p> <p>5 VIDEOGRAPHER: I have another like 15</p> <p>6 minutes.</p> <p>7 MS. PARFITT: Can we take a short</p> <p>8 break, and we'll come back?</p> <p>9 VIDEOGRAPHER: Okay. The time is 5:42</p> <p>10 p.m. We are going off the record.</p> <p>11 (Recess 5:42 to 5:50 p.m.)</p> <p>12</p> <p>13 VIDEOGRAPHER: We are back on the</p> <p>14 record. The time is 5:50 p.m. This is Media Unit No. 5.</p> <p>15</p> <p>16</p> <p>17 EXAMINATION</p> <p>18 BY MS. PARFITT:</p> <p>19 Q Dr. McTiernan, good evening. I just have a few questions</p> <p>20 for you for the Ladies and Gentlemen of the Jury.</p> <p>21 Dr. McTiernan, have you had an opportunity to review</p> <p>22 the Canadian draft screening assessment by Health Canada?</p> <p>23 A I did, yes.</p> <p>24 Q And have you had an opportunity to review the entire</p> <p>25 report?</p>

<p style="text-align: right;">Page 306</p> <p>1 A Yes, I did.</p> <p>2 Q All right. And who sponsored that study?</p> <p>3 A It was Health Canada.</p> <p>4 (Exhibit No. 26 marked</p> <p>5 for identification.)</p> <p>6</p> <p>7 Q (By Ms. Parfitt) All right. I am going to have marked</p> <p>8 as Exhibit No. 26, Dr. McTiernan, a copy of just the</p> <p>9 draft screening assessment, dated December 2018, and,</p> <p>10 again, ask if you will identify that.</p> <p>11 A Yes, Exhibit No. 26.</p> <p>12 Q That is one of the documents you have reviewed?</p> <p>13 A Yes.</p> <p>14 Q Have you reviewed any other documents that are part of</p> <p>15 the Health Canada assessment of talc?</p> <p>16 A There was several other documents that were available.</p> <p>17 These were drafted by the Health Canada for</p> <p>18 information sheets for the public, and one that is called</p> <p>19 "Talc: potential risk of lung effects and ovarian</p> <p>20 cancer," another is a talc information sheet, a third is</p> <p>21 on talc, and, again it's also information for the public</p> <p>22 of how to minimize exposure, so they are already planning</p> <p>23 what the public health messages will be.</p> <p>24 One is a risk management scope, and this is to do</p> <p>25 with the regulatory decisions, and also the Canadian</p>	<p style="text-align: right;">Page 308</p> <p>1 talc can cause ovarian cancer.</p> <p>2 Q (By Ms. Parfitt) Specifically what are you referring to,</p> <p>3 if you will?</p> <p>4 A So on-- are there page numbers on here-- on Page 21 of</p> <p>5 the draft-- document called, "Draft screening</p> <p>6 assessment," in the fourth paragraph down, the third</p> <p>7 line, it says, "Further, available data are indicative of</p> <p>8 a causal effect."</p> <p>9 Another-- also, on Page 29, third paragraph down,</p> <p>10 states that "On the basis of information presented in</p> <p>11 this draft screening assessment, it is proposed to</p> <p>12 conclude that talc meets the criteria under Paragraph</p> <p>13 No. 64C of CEPA as it is entering or may enter the</p> <p>14 environment in a quantity or concentrations or under</p> <p>15 conditions that constitute or may constitute a danger in</p> <p>16 Canada to human life or health."</p> <p>17 Also in the beginning on Page Roman Numeral No. III,</p> <p>18 it states in the fifth paragraph, "The meta-analyses of</p> <p>19 the available human studies in the peer-reviewed</p> <p>20 literature indicate a consistent and statistically</p> <p>21 significant positive association between perineal</p> <p>22 exposure to talc and ovarian cancer. Further, available</p> <p>23 data are indicative of a causal effect."</p> <p>24 Q Dr. McTiernan, from reviewing the draft screening</p> <p>25 assessment performed by Health Canada, were you able to</p>
<p style="text-align: right;">Page 307</p> <p>1 weight of evidence general principles and current</p> <p>2 applications at Health Canada.</p> <p>3 Q Now--</p> <p>4 MR. LOCKE: Objection; nonresponsive,</p> <p>5 move to strike.</p> <p>6 Q (By Ms. Parfitt) Dr. McTiernan, the information from</p> <p>7 Health Canada was made available to you, I believe you</p> <p>8 testified, after your report was submitted in November</p> <p>9 2018; is that correct?</p> <p>10 A That's correct.</p> <p>11 Q All right. And the date, again, of the Health Canada</p> <p>12 assessment was December 2018, correct?</p> <p>13 A Yes, correct.</p> <p>14 Q So at the time you submitted your report in the</p> <p>15 multidistrict litigation, you did not have access to the</p> <p>16 Health Canada report, correct?</p> <p>17 A Correct.</p> <p>18 Q All right. Now, have you-- do you have an opinion, to a</p> <p>19 reasonable degree of scientific certainty, as to whether</p> <p>20 or not Health Canada has opined that talcum powder</p> <p>21 products can cause ovarian cancer?</p> <p>22 MR. WILLIAMS: Objection; lacks</p> <p>23 foundation, calls for speculation.</p> <p>24 THE WITNESS: Health Canada does, in</p> <p>25 several places, firmly state that talcum powder-- that</p>	<p style="text-align: right;">Page 309</p> <p>1 determine whether or not they did indeed perform a</p> <p>2 causality assessment?</p> <p>3 MR. WILLIAMS: Lacks foundation, calls</p> <p>4 for speculation.</p> <p>5 THE WITNESS: They did do a full</p> <p>6 causal analysis that includes information from</p> <p>7 toxicology, animal studies of the biologic information,</p> <p>8 perineal exposure to talc, and then the human studies.</p> <p>9 I am looking for where they did their full</p> <p>10 causation.</p> <p>11 So they then determined characteristic of risk to</p> <p>12 human health, and then came up with their conclusions</p> <p>13 about what-- that further available data are indicative</p> <p>14 of a causal effect.</p> <p>15 Q (By Ms. Parfitt) What methodology did they employ?</p> <p>16 A They did methodology that was similar to what I did for</p> <p>17 my report.</p> <p>18 They reviewed the epidemiologic data from a</p> <p>19 meta-analysis.</p> <p>20 They reviewed the data-- the literature on animal</p> <p>21 studies.</p> <p>22 They reviewed toxicology.</p> <p>23 They reviewed information in how talc can be-- can</p> <p>24 reach the ovary areas, and from that came up with their</p> <p>25 conclusions.</p>

Page 310	Page 312
<p>1 Q Was part of the Health Canada causality assessment a</p> <p>2 study by the name of Tair (phonetic)?</p> <p>3 A Yes. That was the meta-analysis that they reviewed.</p> <p>4 Q Okay. And that was just one part--</p> <p>5 A That was the primary meta-analyses-- the most recent</p> <p>6 meta-analysis that I reviewed.</p> <p>7 Q And that was just one part of the Health Canada</p> <p>8 assessment; is that correct?</p> <p>9 A Exactly.</p> <p>10 Q Dr. McTiernan, you were asked by counsel for J&amp;J whether</p> <p>11 or not it would be repugnant for a company to test their</p> <p>12 talcum powder products for asbestos.</p> <p>13 Do you remember that question?</p> <p>14 A I believe the question was posed-- I would have to review</p> <p>15 the question again.</p> <p>16 I believe there was something about brakes and</p> <p>17 another--</p> <p>18 Q Let me just--</p> <p>19 A I think the category was talcum testing for asbestos.</p> <p>20 Q I believe the question was whether-- first, whether it</p> <p>21 was repugnant for a company to test for asbestos, whether</p> <p>22 J&amp;J would be repugnant for them to test-- to actually do</p> <p>23 testing of their product.</p> <p>24 Do you recall that?</p> <p>25 A Yes.</p>	<p>1 VIDEOGRAPHER: This marks the end of</p> <p>2 today's video deposition. The time is 5:59 p.m.</p> <p>3 (Deposition concluded at 5:59 p.m.)</p> <p>4 (Signature reserved.)</p> <p>5</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
Page 311	Page 313
<p>1 Q And he then asked you whether it was repugnant if a brake</p> <p>2 company also tested to determine whether or not their</p> <p>3 products' brakes failed.</p> <p>4 Do you remember that?</p> <p>5 A Yes.</p> <p>6 Q In your opinion would it be repugnant for a company, if</p> <p>7 they found that the brakes had failed, to not inform the</p> <p>8 public?</p> <p>9 A Yes.</p> <p>10 MR. WILLIAMS: Incomplete</p> <p>11 hypothetical.</p> <p>12 MR. LOCKE: Just note my objection.</p> <p>13 Q (By Ms. Parfitt) Similarly, would it be repugnant of a</p> <p>14 manufacturing company or a supplier who tested their</p> <p>15 product and found asbestos to not warn or communicate</p> <p>16 with the public and the medical and scientific field</p> <p>17 about the fact that their product had asbestos?</p> <p>18 MR. WILLIAMS: Same objection.</p> <p>19 MS. ERFLE: Objection; also lacks</p> <p>20 foundation.</p> <p>21 THE WITNESS: Yes.</p> <p>22 MS. PARFITT: I have no further</p> <p>23 questions, Dr. McTiernan. Thank you.</p> <p>24 MR. WILLIAMS: I think that's it--</p> <p>25 actually-- that's fine.</p>	<p>1 STATE OF WASHINGTON ) I, Terilynn Simons, CCR, RMR, CRR</p> <p>2 ) ss a certified court reporter</p> <p>3 County of Pierce ) in the State of Washington, do</p> <p>4 hereby certify:</p> <p>5</p> <p>6 That the foregoing deposition of ANNE MCTIERNAN, PH.D.</p> <p>7 was taken before me and completed on January 28, 2019, and</p> <p>8 thereafter was transcribed under my direction; that the</p> <p>9 deposition is a full, true and complete transcript of the</p> <p>10 testimony of said witness, including all questions, answers,</p> <p>11 objections, motions and exceptions;</p> <p>12 That the witness, before examination, was by me duly</p> <p>13 sworn to testify the truth, the whole truth, and nothing but</p> <p>14 the truth, and that the witness reserved the right of</p> <p>15 signature;</p> <p>16</p> <p>17 That I am not a relative, employee, attorney or counsel</p> <p>18 of any party to this action or relative or employee of any</p> <p>19 such attorney or counsel and that I am not financially</p> <p>20 interested in the said action or the outcome thereof;</p> <p>21 That I am herewith securely sealing the said deposition</p> <p>22 and promptly delivering the same to Bart H. Williams.</p> <p>23</p> <p>24 IN WITNESS WHEREOF, I have hereunto set my signature on</p> <p>25 the 30th day of January, 2019.</p> <p>26</p> <p>27</p> <p>28</p> <p>29</p> <p>30</p> <p>31</p> <p>32</p> <p>33</p> <p>34</p> <p>35</p> <p>Terilynn Simons, CCR, RMR, CRR Certified Court Reporter No. 2047 (Certification expires 07/07/19.)</p>

1	-----
2	ERRATA
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4	PAGE LINE CHANGE
5	_____
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1	ACKNOWLEDGMENT OF DEPONENT
2	
3	I, _____, do
4	hereby certify that I have read the
5	foregoing pages, and that the same
6	is a correct transcription of the answers
7	given by me to the questions therein
8	propounded, except for the corrections or
9	changes in form or substance, if any,
10	noted in the attached Errata Sheet.
11	
12	_____
13	ANNE MCTIERNAN, PH.D.      DATE
14	
15	Subscribed and sworn
16	to before me this
17	_____ day of _____, 20____.
18	My commission expires: _____
19	_____
20	Notary Public
21	
22	
23	
24	
25	



# Exhibit 60

# Introduction to Meta-Analysis

**Michael Borenstein**

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**Larry V. Hedges**

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**Hannah R. Rothstein**

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### Impact of Statin Dose On Death and Myocardial Infarction

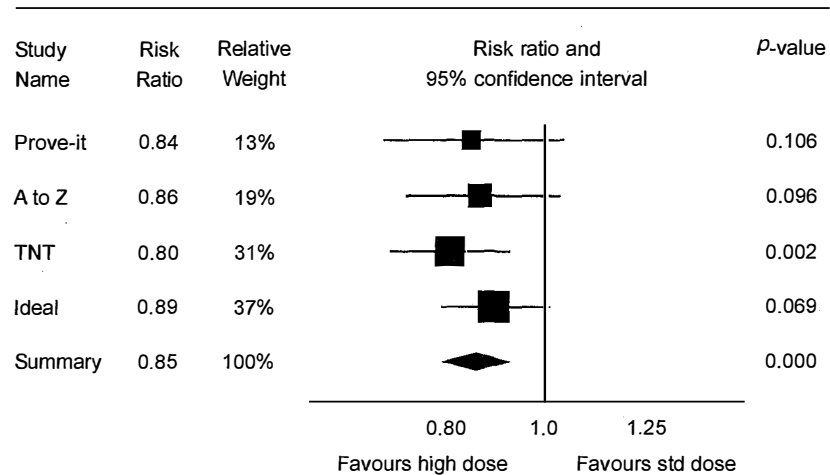


Figure 1.1 High-dose versus standard-dose of statins (adapted from Cannon *et al.*, 2006).

work with the effect sizes to assess the consistency of the effect across studies and to compute a summary effect.

The effect size could represent the impact of an intervention, such as the impact of medical treatment on risk of infection, the impact of a teaching method on test scores, or the impact of a new protocol on the number of salmon successfully returning upstream. The effect size is not limited to the impact of interventions, but could represent *any relationship* between two variables, such as the difference in test scores for males versus females, the difference in cancer rates for persons exposed or not exposed to second-hand smoke, or the difference in cardiac events for persons with two distinct personality types. In fact, what we generally call an *effect size* could refer simply to the estimate of a single value, such as the prevalence of Lyme disease.

In this example the effect size is the risk ratio. A risk ratio of 1.0 would mean that the risk of death or MI was the same in both groups, while a risk ratio less than 1.0 would mean that the risk was lower in the high-dose group, and a risk ratio greater than 1.0 would mean that the risk was lower in the standard-dose group.

The effect size for each study is represented by a square, with the location of the square representing both the direction and magnitude of the effect. Here, the effect size for each study falls to the left of center (indicating a benefit for the high-dose group). The effect is strongest (most distant from the center) in the *TNT* study and weakest in the *Ideal* study.

Note. For measures of effect size based on ratios (as in this example) a ratio of 1.0 represents no difference between groups. For measures of effect based on differences (such as mean difference), a difference of 0.0 represents no difference between groups.

effect size to the right of center indicates that control patients were more likely to survive.

The plot serves to highlight the following points.

- The effect sizes are reasonably consistent from study to study. Most fall in the range of 0.50 to 0.90, which suggests that it would be appropriate to compute a summary effect size.
- The summary effect is a risk ratio of 0.79 with a 95% confidence interval of 0.72 to 0.87 (that is, a 21% decrease in risk of death, with 95% confidence interval of 13% to 28%). The  $p$ -value for the summary effect is 0.0000008.
- The confidence interval that bounds each effect size indicates the precision in that study. If the interval excludes 1.0, the  $p$ -value is less than 0.05 and the study is statistically significant. Six of the studies were statistically significant while 27 were not.

In sum, the treatment reduces the risk of death by some 21%. And, this effect was reasonably consistent across all studies in the analysis.

Over the course of this volume we explain the statistical procedures that led to these conclusions. Our goal in the present chapter is simply to explain that meta-analysis does offer these mechanisms, whereas the narrative review does not. The key differences are as follows.

### STATISTICAL SIGNIFICANCE

One of the first questions asked of a study is the statistical significance of the results. The narrative review has no mechanism for synthesizing the  $p$ -values from the different studies, and must deal with them as discrete pieces of data. In this example six of the studies were statistically significant while the other 27 were not, which led some to conclude that there was evidence against an effect, or that the results were inconsistent (see vote counting in Chapter 28). By contrast, the meta-analysis allows us to combine the effects and evaluate the statistical significance of the summary effect. The  $p$ -value for the summary effect is  $p = 0.0000008$ .

While one might assume that 27 studies failed to reach statistical significance because they reported small effects, it is clear from the forest plot that this is not the case. In fact, the treatment effect in many of these studies was actually *larger* than the treatment effect in the six studies that *were* statistically significant. Rather, the reason that 82% of the studies were not statistically significant is that these studies had small sample sizes and low statistical power. In fact, as discussed in Chapter 29, most had power of less than 20%. By contrast, power for the meta-analysis exceeded 99.9% (see Chapter 29).

As in this example, if the goal of a synthesis is to test the null hypothesis, then meta-analysis provides a mathematically rigorous mechanism for this purpose. However, meta-analysis also allows us to move beyond the question of



statistical significance, and address questions that are more interesting and also more relevant.

### CLINICAL IMPORTANCE OF THE EFFECT

Since the point of departure for a narrative review is usually the  $p$ -values reported by the various studies, the review will often focus on the question of whether or not the body of evidence allows us to reject the null hypothesis. There is no good mechanism for discussing the magnitude of the effect. By contrast, the meta-analytic approaches discussed in this volume allow us to compute an estimate of the effect size for each study, and these effect sizes fall at the core of the analysis.

This is important because the effect size is what we care about. If a clinician or patient needs to make a decision about whether or not to employ a treatment, they want to know if the treatment reduces the risk of death by 5% or 10% or 20%, and this is the information carried by the effect size. Similarly, if we are thinking of implementing an intervention to increase the test scores of students, or to reduce the number of incarcerations among at-risk juveniles, or to increase the survival time for patients with pancreatic cancer, the question we ask is about the magnitude of the effect. The  $p$ -value can tell us only that the effect is not zero, and to report simply that the effect is not zero is to miss the point.

### CONSISTENCY OF EFFECTS

When we are working with a collection of studies, it is critically important to ask whether or not the effect size is consistent across studies. The implications are quite different for a drug that consistently reduces the risk of death by 20%, as compared with a drug that reduces the risk of death by 20% on average, but that increases the risk by 20% in some populations while reducing it by 60% in others.

The narrative review has no good mechanism for assessing the consistency of effects. The narrative review starts with  $p$ -values, and because the  $p$ -value is driven by the size of a study as well as the effect in that study, the fact that one study reported a  $p$ -value of 0.001 and another reported a  $p$ -value of 0.50 does not mean that the effect was larger in the former. The  $p$ -value of 0.001 *could* reflect a large effect size but it could also reflect a moderate or small effect in a large study (see the GISSI-1 study in Figure 2.1, for example). The  $p$ -value of 0.50 *could* reflect a small (or nil) effect size but could also reflect a large effect in a small study (see the Fletcher study, for example).

This point is often missed in narrative reviews. Often, researchers interpret a nonsignificant result to mean that there is no effect. If some studies are statistically significant while others are not, the reviewers see the results as conflicting. This problem runs through many fields of research. To borrow a phrase from Cary Grant's character in *Arsenic and Old Lace*, we might say that it practically gallops.

the results, and therefore we should not assume a common effect size. Therefore, in these cases the random-effects model is more easily justified than the fixed-effect model.

Additionally, the goal of this analysis is usually to generalize to a range of scenarios. Therefore, if one did make the argument that all the studies used an identical, narrowly defined population, then it would not be possible to extrapolate from this population to others, and the utility of the analysis would be severely limited.

#### A caveat

There is one caveat to the above. If the number of studies is very small, then the estimate of the between-studies variance ( $\tau^2$ ) will have poor precision. While the random-effects model is still the appropriate model, we lack the information needed to apply it correctly. In this case the reviewer may choose among several options, each of them problematic.

One option is to report the separate effects and *not* report a summary effect. The hope is that the reader will understand that we cannot draw conclusions about the effect size and its confidence interval. The problem is that some readers will revert to vote counting (see Chapter 28) and possibly reach an erroneous conclusion.

Another option is to perform a fixed-effect analysis. This approach would yield a descriptive analysis of the included studies, but would not allow us to make inferences about a wider population. The problem with this approach is that (a) we do want to make inferences about a wider population and (b) readers will make these inferences even if they are not warranted.

A third option is to take a Bayesian approach, where the estimate of  $\tau^2$  is based on data from outside of the current set of studies. This is probably the best option, but the problem is that relatively few researchers have expertise in Bayesian meta-analysis. Additionally, some researchers have a philosophical objection to this approach.

For a more general discussion of this issue see *When does it make sense to perform a meta-analysis* in Chapter 40.

#### MODEL SHOULD NOT BE BASED ON THE TEST FOR HETEROGENEITY

In the next chapter we will introduce a test of the null hypothesis that the between-studies variance is zero. This test is based on the amount of between-studies variance observed, relative to the amount we would expect if the studies actually shared a common effect size.

Some have adopted the practice of starting with a fixed-effect model and then switching to a random-effects model if the test of homogeneity is statistically significant. This practice should be strongly discouraged because the decision to use the random-effects model should be based on our understanding of whether or not all studies share a common effect size, and not on the outcome of a statistical test (especially since the test for heterogeneity often suffers from low power).

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## CHAPTER 28

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# Vote Counting – A New Name for an Old Problem

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### Introduction

Why vote counting is wrong

Vote counting is a pervasive problem

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### INTRODUCTION

One question we often ask of the data is whether or not it allows us to reject the null hypothesis of no effect. Researchers who address this question using a narrative review need to synthesize the  $p$ -values reported by the separate studies. Since these are discrete pieces of information and the narrative review provides no statistical mechanism for synthesizing these values, narrative reviewers often resort to a process called vote counting. Under this process the reviewer counts the number of statistically significant studies and compares this with the number of statistically nonsignificant studies.

In some cases this process has been formalized, such that one actually counts the number of significant and nonsignificant  $p$ -values and picks the winner. In some variants, the reviewer would look for a clear majority rather than a simple majority. Or, the reviewer might not work directly with the  $p$ -values, but with the discussion section of the papers which are based on the  $p$ -values.

One might think that summarizing  $p$ -values through a vote-counting procedure would yield more accurate decision than any one of the single significance tests being summarized. This is not generally the case, however. In fact, Hedges and Olkin (1980) showed that the power of vote-counting considered as a statistical decision procedure can not only be lower than that of the studies on which it is based, the power of vote counting can tend toward zero as the number of studies increases. In other words, vote counting is not only misleading, it tends to be *more* misleading as the amount of evidence (the number of studies) increases!

In any event, the idea of vote counting is fundamentally flawed and the variants on this process are equally flawed (and perhaps even more dangerous, since the basic flaw is less obvious when hidden behind a more complicated algorithm or is one step removed from the  $p$ -value). Our goal in this chapter is to explain why this is so, and to provide a few examples.

### WHY VOTE COUNTING IS WRONG

The logic of vote counting says that a significant finding is evidence that an effect exists, while a nonsignificant finding is evidence that an effect is absent. While the first statement is true, the second is not. While a nonsignificant finding *could* be due to the fact that the true effect is nil, it can also be due simply to low statistical power.

Put simply, the  $p$ -value reported for any study is a function of the observed effect size and the sample size. Even if the observed effect is substantial, the  $p$ -value will not be significant unless the sample size is adequate. In other words, as most of us learned in our first statistics course, *the absence of a statistically significant effect is not evidence that an effect is absent*.

For example, suppose five randomized controlled trials (RCTs) had been performed to test the impact of an intervention, and that none were statistically significant (the  $p$ -value in each case is 0.265) as illustrated in Figure 28.1. The vote count is 5 to 0 against an effect, and one might assume that the intervention has no effect.

By contrast, the meta-analysis (Figure 28.1), by combining the information into a single analysis, allows us to perform a proper test of the null. Not only is this approach valid, but the test of the summary effect is often much more powerful than tests performed on any of the separate studies. When we merge the data, the effect size stays the same, but the confidence interval narrows and no longer includes the null. The  $p$ -value for each study alone is 0.265, but the  $p$ -value for the summary effect is

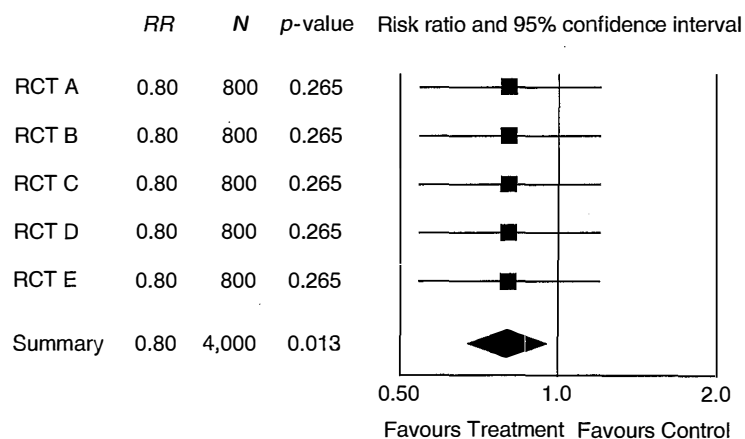


Figure 28.1 The  $p$ -value for each study is  $> 0.20$  but the  $p$ -value for the summary effect is  $< 0.02$ .



0.013. Clearly, the absence of significance in each study is due to a lack of precision rather than a small effect.

For purposes of explaining why vote counting is a bad idea, we could end the chapter here. However, because vote counting in its various forms is so pervasive, we will expand on this idea to show how the basic mistake that underlies vote counting affects much of the literature, and how meta-analysis can help address this problem.

### VOTE COUNTING IS A PERVASIVE PROBLEM

While the term vote counting is associated with narrative reviews it can also be applied to the single study, where a significant  $p$ -value is taken as evidence that an effect exists, and a nonsignificant  $p$ -value is taken as evidence that an effect does not exist. Numerous surveys in a wide variety of substantive fields have repeatedly documented the ubiquitous nature of this mistake.

In medicine, for example, Freiman, Chalmers, Smith and Kuebler (1978) surveyed reports of controlled clinical trials that had been published in a number of medical journals (primarily *The Lancet*, the *New England Journal of Medicine*, and the *Journal of the American Medical Association* during the period 1960–1977), and selected 71 that had reported negative results. The authors found that if the true drug effect had been in the region of 50% (e.g. a mortality rate of 30% for placebo vs. 15% for drug), median power would have been 60%. In other words, even if the drug cut the mortality rate in half there was still a 40% probability that the study would have failed to obtain a statistically significant result.

The authors went on to make the following point: Despite the fact that power was terribly low, in most cases the absence of statistical significance was interpreted as meaning that the drug *was not effective*. They wrote: ‘The conclusion is inescapable that many of the therapies discarded as ineffective after inconclusive “negative” trials may still have a clinically meaningful effect’ (p. 694). In fact, it is possible (or likely) that some of the therapies discarded on this basis might well have had very substantial therapeutic effects.

In the social sciences Cohen (1962) surveyed papers published in the *Journal of Abnormal and Social Psychology* in 1960. Mean power to detect a small, medium, or large effect, respectively, was 0.18, 0.48, and 0.83. Cohen noted that despite the low power, when the studies with *negative* results are published, readers tend to interpret the absence of statistical significance as evidence that the treatment has been proven ineffective.

In the years that followed a kind of cottage industry developed of publishing papers that documented the fact of low power in any number of journals in the area of behavioral research. Many of these are cited in Sedlmeier and Gigerenzer (1989) and Rossi (1990). Similar papers were published to document the same problem in the field of medicine (Borenstein, 1994; Hartung, Cottrell & Giffen, 1983; Phillips,



Scott, & Blasczynski, 1983; Reed & Slaichert, 1981; Reynolds, 1980) and psychiatry (Kane & Borenstein, 1985).

Sedlmeier and Gigerenzer (1989) published a paper entitled *Do studies of statistical power have an effect on the power of statistical studies?* They found that in the 25 years since Cohen's initial survey power had not changed in any substantive way. Similarly, Rossi (1990) reviewed papers published in 1982 in the *Journals of Abnormal Psychology, Consulting and Clinical Psychology, and Personality and Social Psychology*. Mean power to detect small, medium, and large effects, respectively, was 0.17, 0.57, and 0.83.

This led one of the current authors (Borenstein, 2000) to propose four theorems, as follows.

1. Power in many fields of research is abysmally low.
2. Rule (1) appears to be impervious to change.
3. The absence of significance should be interpreted as *more information is required* but is interpreted in error as meaning *no effect exists*.
4. Rule (3) appears to be impervious to change.

In a sense, then, vote counting did not originate with the narrative review. Rather, the basic mistake has existed for decades, where it found a home in primary research. When the field moved on to narrative reviews, this basic mistake was named and codified but remained basically unchanged.

There is, however, one important difference. When we are working with a single study and we have a nonsignificant result we don't have any way of knowing whether or not the effect is real. The nonsignificant *p*-value could reflect either the fact that the true effect is nil *or* the fact that our study had low power. While we caution against accepting the former (that the true effect is nil) we cannot rule it out.

By contrast, when we use meta-analysis to synthesize the data from a series of studies we can often identify the true effect. And in many cases (for example if the true effect is substantial and is consistent across studies) we can assert that the nonsignificant *p*-value in the separate studies was due to low power rather than the absence of an effect.

In the streptokinase meta-analysis on page 10, for example, it is clear that the treatment does reduce the risk of death. It is fair to say that the reason that 27 studies had nonsignificant *p*-values was *not* because the treatment had no effect, but rather was because of low statistical power. (In the next chapter we actually compute the power for the streptokinase studies.)

### Moving beyond the null

In this chapter we have shown that *if our goal* is to test the null hypothesis, then meta-analysis (unlike the narrative review) provides a statistically sound mechanism for this purpose. However, we want to emphasize that meta-analysis allows us

to move beyond a test of the null. It allows us to assess the magnitude of the effect (which is often a more relevant question) and to determine whether or not the effect size is consistent across studies.

**SUMMARY POINTS**

- Vote counting is the process of counting the number of studies that are statistically significant and comparing this with the number that are not statistically significant.
- Vote counting treats a nonsignificant  $p$ -value as evidence that an effect is absent. In fact, though, small, moderate, and even large effect sizes may yield a nonsignificant  $p$ -value due to inadequate statistical power. Therefore, vote counting is never a valid approach.

unpublished, research lies dormant in the researchers' filing cabinets, and has led to the use of the term *file drawer problem* for meta-analysis.

### Response

Since published studies are more likely to be included in a meta-analysis than their unpublished counterparts, there is a legitimate concern that a meta-analysis may overestimate the true effect size.

Chapter 30 (entitled *Publication Bias*) explores this question in some detail. In that chapter we discuss methods to assess the likely amount of bias in any given meta-analysis, and to distinguish between analyses that can be considered robust to the impact of publication bias from those where the results should be considered suspect.

We must remember that publication bias is a problem for any kind of literature search. The problem exists for the clinician who searches a database to locate primary studies about the utility of a treatment. It exists for persons performing a narrative review. And, it exists for persons performing a meta-analysis. Publication bias has come to be identified with meta-analysis because meta-analysis has the goal of providing a more accurate synthesis than other methods, and so we are concerned with biases that will interfere with this goal. However, it would be a mistake to conclude that this bias is not a problem for the narrative review. There, it is simply easier to ignore.

## MIXING APPLES AND ORANGES

### Criticism

A common criticism of meta-analysis is that researchers combine different kinds of studies (*apples and oranges*) in the same analysis. The argument is that the summary effect will ignore possibly important differences across studies.

### Response

The studies that are brought together in a meta-analysis will inevitably differ in their characteristics, and the difficulty is deciding just how similar they need to be. The decision as to which studies should be included is always a judgment, and people will have different opinions on the appropriateness of combining results across studies. Some meta-analysts may make questionable judgments, and some critics may make unreasonable demands on similarity.

We need to remember that meta-analyses almost always, by their very nature, address broader questions than individual studies. Hence a meta-analysis may be thought of as asking a question about fruit, for which both apples and oranges (and indeed pears and melons) contribute valuable information. One of the strengths of meta-analysis is that the consistency, and hence generalizability, of findings from one type of study to the next can be assessed formally.

Of course, we always need to remember that we are dealing with different kinds of fruit, and to anticipate that effects may vary from one kind to the other. It is a further strength of meta-analysis that these differences, if identified, can be investigated formally. Assume, for example, that a treatment is very effective for patients with acute symptoms but has no effect for patients with chronic symptoms. If we were to combine data from studies that used both types of patients, and conclude that the treatment was modestly effective (on average), this conclusion would not be accurate for either kind of patient. If we were to restrict our attention to studies in only patients with acute symptoms, or only patients with chronic symptoms, we could report how the treatment worked with one type of patient, but could only speculate about how it would have worked with the other type. By contrast, a meta-analysis that includes data for both types of patients may allow us to address this question empirically.

### GARBAGE IN, GARBAGE OUT

#### Criticism

The often-heard metaphor *garbage in, garbage out* refers to the notion that if a meta-analysis includes many low-quality studies, then fundamental errors in the primary studies will be carried over to the meta-analysis, where the errors may be harder to identify.

#### Response

Rather than thinking of meta-analysis as a process of *garbage in, garbage out* we can think of it as a process of waste management. A systematic review or meta-analysis will always have a set of inclusion criteria and these should include criteria based on the quality of the study. For trials, we may decide to limit the studies to those that use random assignment, or a placebo control. For observational studies we may decide to limit the studies to those where confounders were adequately addressed in the design or analysis. And so on. In fact, it is common in a systematic review to start with a large pool of studies and end with a much smaller set of studies after all inclusion/exclusion criteria are applied.

Nevertheless, the studies that do make it as far as a meta-analysis are unlikely to be perfect, and close attention should be paid to the possibility of bias due to study limitations. A meta-analysis of a collection of studies that is each biased in the same direction will suffer from the same bias and have higher precision. In this case, performing a meta-analysis can indeed be more dangerous than not performing one.

However, as noted in the response to the previous criticism about *apples and oranges*, a strength of meta-analysis is the ability to investigate whether variation in characteristics of studies is related to the size of the effect. Suppose that ten studies used an acceptable method to randomize patients while another ten used a questionable method. In the analysis we can compare the effect size in these two subgroups, and determine whether or not the effect size actually differs between

the two. Note that such analyses (those comparing effects in different subgroups) can have very low power so need to be interpreted carefully, especially when there are not many studies within subgroups.

### IMPORTANT STUDIES ARE IGNORED

#### Criticism

Whereas the *garbage in, garbage out* problem relates to the inclusion of studies that perhaps should not be included, a common complementary criticism is that important studies were left out. The criticism is often leveled by people who are uncomfortable with the findings of a meta-analysis. For example, a meta-analysis to assess the effects of antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) on overall mortality was met with accusations on the web site of the Linus Pauling Institute (Oregon State University) that in this 'flawed analysis of flawed data' the authors looked at 815 human clinical trials of antioxidant supplements, but only 68 were included in the meta-analysis.

#### Response

We have explained that systematic reviews and meta-analyses require explicit mechanisms for deciding which studies to include and which ones to exclude. These eligibility criteria are determined by a combination of considerations of relevance and considerations of bias, and are typically decided before the search for studies is implemented. Studies should be sufficiently similar to yield results that can be interpreted, and sufficiently free of bias to yield results that can be believed. For both purposes, judgments are required, and not all meta-analysts or readers would reach the same judgments on each occasion. Importantly, in meta-analysis the criteria are transparent and are described as part of the report.

### META-ANALYSIS CAN DISAGREE WITH RANDOMIZED TRIALS

#### Criticism

LeLorier *et al.* (1997) published a paper in which they pointed out that meta-analyses sometimes yield different results than large scale randomized trials. Specifically, they located cases in the medical literature where someone had performed a meta-analysis, and someone else subsequently performed a large scale randomized trial that addressed the same question (e.g. *Does the treatment work?*). The authors reported that the results of the meta-analysis and the randomized trial *matched* (both were statistically significant, or neither was statistically significant) in about 66% of cases, but did not match (one was statistically significant but the other was not) in the remaining 34%. Since randomized trials are generally accepted as the gold standard they conclude that some 34% of these meta-analyses were wrong, and that meta-analyses in general cannot be trusted.



# Exhibit 61

[Hide Cover](#)**European Journal of Cancer Prevention**

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Publication Type: [Review Article: Gynecological Cancer]

[Review Article: Gynecological Cancer]

**Genital use of talc and risk of ovarian cancer: a meta-analysis**Berge, Wera<sup>a</sup>; Mundt, Kenneth<sup>b</sup>; Luu, Hung<sup>c</sup>; Boffetta, Paolo<sup>d</sup>**Author Information**<sup>a</sup>Faculty of Medicine, University of Dresden, Dresden, Germany<sup>b</sup>Ramboll Environ, Amherst, Massachusetts<sup>c</sup>University of South Florida College of Public Health, Tampa, Florida<sup>d</sup>Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, New York, USA

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**Abstract**

Some epidemiological studies suggest an association between genital use of talc powders and increased risk of ovarian cancer, but the evidence is not consistent. We performed a meta-analysis of epidemiological studies to formally evaluate this suspected association. A systematic search was conducted in Medline, Embase, and Scopus, leading to the identification of 24 case–control studies and three cohort studies. In the meta-analysis, we used a random-effect model to calculate summary estimates of the association between genital use of talc and occurrence of ovarian cancer. We assessed potential sources of between-study heterogeneity and presence of publication bias. The summary relative risk (RR) for ever use of genital talc and ovarian cancer was 1.22 [95% confidence interval (CI): 1.13–1.30]. The RR for case–control studies was 1.26 (95% CI: 1.17–1.35) and for cohort studies was 1.02 (95% CI: 0.85–1.20,  $P_{\text{heterogeneity}}=0.007$ ). Serous carcinoma was the only histologic type for which an association was detected (RR: 1.24; 95% CI: 1.15–1.34). There was a weak trend in RR with duration and frequency of genital talc use. This meta-analysis resulted in a weak but statistically significant association between genital use of talc and ovarian cancer, which appears to be limited to serous carcinoma with suggestion of dose-response. The heterogeneity of results by study design however, detracts from a causal interpretation of this association.

**Introduction**

With over 22 000 new cases diagnosed and about 14 000 deaths every year in the USA alone, ovarian cancer ranks as the fifth as a cause of neoplastic death among women. It accounts for more deaths than from any other cancer of the female reproductive system, although incidence numbers decreased since the mid-1980s ([American Cancer Society, 2016](#)). Most ovarian cancers are detected at a later stage and have limited prospects of cure. This is mainly because of the lack of a screening method for its detection at an early stage and resistance against chemotherapy. The etiology of the disease is not fully understood, although researchers have identified several risk factors, including a family history of ovarian or breast cancer, advanced age, white race, nulliparity, obesity, education level, and endometriosis ([Kim et al., 2014](#)). In addition, breast feeding, tubal ligation, and oral contraceptive use have been reportedly associated with reduced risk ([Webb et al., 2008](#)). Ovarian cancer is a heterogeneous disease that comprises four major histologic types; serous carcinoma is the most common form (50%), followed by mucinous, endometrioid, and clear cell carcinoma. Each type, with the exception of clear cell carcinoma, is divided into grades of malignancy ([Wang et al., 2005](#)). On the basis of limited data, there appears to be some heterogeneity in risk factors for specific histologic types ([Chiaffarino et al., 2007](#); [Gates et al., 2010](#)).

An association between exposure to asbestos and increased risk of ovarian cancer has been reported ([Reid et al., 2011](#)), but it remains unclear whether this might reflect misclassification of peritoneal mesothelioma, a disease linked to high exposure to asbestos, or direct action of asbestos fibers on the ovary ([Merino, 2010](#)).

Talc is a naturally occurring mineral that is commonly used in bath and body powders as well as other cosmetic products. Talc naturally occurs as soft crystals that give it a soft, slippery feel, absorbency, softness, and resistance to clumping. It is often applied to sanitary napkins, condoms, or underwear, as well as directly to the genital area. To our knowledge, accurate estimates of prevalence of cosmetic talc use in the genital area are not available. However, the use of powders for female hygiene, including body or deodorizing powders containing cosmetic talc has been reported to be as high as 50% in some regions ([International Agency for Research on Cancer \(IARC\), 2010](#)), including parts of North America, Australia, and the UK.

Since 1982, when the first case-control study reported an association between genital talc and ovarian cancer, interest in genital talc use and risk of ovarian cancer has grown ([Cramer et al., 1982](#)). The use of talcum powder in the genital area had been suggested as a potential risk factor for ovarian cancer based, in part, on a possible structural analogy with asbestos ([Cramer et al., 1982](#)) or the possible contamination by asbestos of some talcum powders in the past ([Cralley et al., 1968](#)). However, the structural similarities between asbestos minerals in the crystalline fiber form (i.e. asbestos habit) and structures seen microscopically in talcum that resemble fibers such as 'ribbons' of talc crystals or cleavage fragments of talc or other minerals, are few. Furthermore, talcum powders for domestic use in the USA have been virtually asbestos-free since the 1970s ([Rohl et al., 1976](#)).

Several more recent case-control studies have reported associations between ovarian cancer and self-reported genital talcum powder use. However, the association between talc use and ovarian cancer risk reported in case-control studies has not been limited to studies in which genital talcum powder use occurred before cosmetic products were known to be asbestos-free. It has been suggested that talcum powder may be directly carcinogenic to the ovaries, provided that talc particles may be able to travel through the female reproductive system to the ovaries ([Heller et al., 1996](#)). In one study, talc-like particles were detected more frequently in ovarian tumors than in normal human ovarian tissue, although the authors of this study emphasized that this study could not determine whether these particles actually caused the malignancy ([Henderson et al., 1979](#)).

Results of epidemiological studies reported during the last three decades have not been consistent ([Huncharek et al., 2007](#); [Terry et al., 2013](#); [Houghton et al., 2014](#)). It remains unclear whether a statistical association exists, and, if so, whether it can be interpreted as reflecting some form of bias or a causal relationship. We performed a systematic review and meta-analysis aiming at providing stronger evidence in favor or against the hypothesis of a causal association between genital talc use and risk of ovarian cancer.

## Methods

We performed a systematic review and meta-analysis on the association between genital talc powder use and the risk of ovarian cancer. Our work was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines ([Liberati et al., 2009](#)). A study protocol was developed in advance, outlining the procedure and methods (available upon request).

## Search strategy

A series of literature searches was conducted in June 2016 using the electronic databases Medline (by PubMed), Embase, and Scopus. There was no limitation on year of publication. We included relevant studies that met the following criteria: papers had to be published in peer-reviewed journals as an original report; had to present novel information on the relation between genital powder use and ovarian cancer, and had to be written in English, German, Italian, French or Spanish. As there are different types of genital powders, we defined genital powder as any type of powder that is applied to the genital, rectal or perineal area, such as talc, baby, deodorizing, cornstarch, or powder of unknown type. We excluded review articles, abstracts, editorials or letters to the editor not including original data, and other studies not meeting the selection criteria.

The following keywords were used for the searches on Medline and Scopus: 'perineal powder' or 'talcum powder' or 'genital powder' and 'ovarian cancer.' For Embase we used the following combination of keywords: 'perineum' or 'talc' and 'ovarian cancer.' In addition, all references cited in the identified papers and reviews were hand-searched for potentially relevant studies that were not captured by the electronic database search.

### Study selection

Titles and abstracts were examined independently by two of the authors (W.B., P.B.). Duplicates and irrelevant references were eliminated. In case of disagreement or doubt the abstracts or articles were discussed until consensus was reached. In case of overlap of results between publications the selection of results was on the basis of the largest population or most detailed analysis, resulting in the exclusion of some publications which were superseded by more recent reports ([Harlow et al., 1992](#); [Cramer et al., 1999](#); [Pike et al., 2004](#)).

### Data extraction

All data of the included studies were extracted by one author (W.B.) and checked by another author (P.B.). Possible disagreements were discussed and solved.

The following data were extracted from each study for the meta-analysis: first author and publication year; study design; study region; period of enrollment; survey instrument; assessment of ovarian cancer; age range; numbers of women with ovarian cancer and those without in case-control studies; numbers of cases of ovarian cancer, sample size and a number of person-years in cohort studies; adjustment for potential confounding factors; outcome by talc exposure (yes/no); duration (years); frequency (times/week); timing of use (early/late); type of talc exposure (sanitary napkin, diaphragm, genital deodorant, cornstarch, use by the partner); endometriosis; surgery (hysterectomy and/or tubal ligation); number of powder applications; characteristics of the participants; and tumor histology and behavior.

### Quality assessment

Every included article was scored for its quality according to a standardized checklist. We used the Newcastle–Ottawa Scale (NOS) case-control checklist and the NOS cohort study checklist for both study types, respectively ([Stang, 2010](#)). The NOS assesses three dimensions of quality: selection, comparability, and exposure (for a case-control study) or outcome (for a cohort study). It assigns a maximum of four points for selection, two points for comparability, and three points for exposure or outcome. Studies with at least seven points were considered of high quality (Supplementary Table 1, Supplemental digital content 1,

<http://links.lww.com/EJCP/A138>

and Table 2, Supplemental digital content 2,

<http://links.lww.com/EJCP/A139>

).

### Statistical analyses

The measure of association of interest was the relative risk (RR) for prospective cohort studies, and the odds ratio (OR) for the case-control studies, with corresponding 95% confidence intervals (CIs). The main meta-analysis compared ever versus never use of genital talc; additional analyses addressed use of powder on sanitary napkins and diaphragms, two potential sources of talc exposure. If results were reported only by categories of exposure, indicators of ever talc use were derived using fixed-effect meta-analyses. Risk estimates were abstracted from each study for comparable exposure categories. An overall pooled RR was then estimated, together with its 95% CI, on the basis of individual estimates from each study. Each study was given a weight on the basis of the inverse of the variance of the effect estimate. We pooled data on different exposures when at least four studies provided sufficient data. A random-effects model was used in the meta-analyses comprising multiple studies, because of the heterogeneity in study design and analysis (DerSimonian and Laird, 1986). The  $I^2$ -statistic was used to assess the percentage of between-study variability that is because of heterogeneity rather than chance (Higgins et al., 2003).

Stratified meta-analyses were conducted for ever genital use of talc according to study design (case-control vs. cohort studies), as well as tumor histology and behavior. Because of the fact that cosmetic talc may have been contaminated by asbestos before the 1970s, when voluntary guidelines were adopted, we compared the results on use in an 'early' and in a 'late' period: the exact cut-point varied across the studies but in general referred to 1970 or 1980.

Meta-regression analyses were performed to obtain overall risk estimates for duration (RR for 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency), for the studies reporting at least three categories of duration or frequency of use. Study-specific slopes were first derived from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model.

The presence and extent of publication bias were assessed visually using funnel plots and evaluated statistically using the Egger's test (Egger et al., 1997). A cumulative meta-analysis was also performed by repeating the calculation of the summary RR and CI (on the basis of a random-effects model) each year a new study was published. When an article superseded a previous article from the same study, the results reported in the earlier report were replaced by the new results.

Analyses were performed using the commands *metan*, *gls*, *metafunnel*, and *metabias* of the statistical software STATA, version 14 (StataCorp, 2015).

## Results

The process of selection of relevant studies is shown in Fig. 1. The electronic searches resulted in a total of 435 articles, of which 150 overlapped between searches. After the exclusion of the duplicates and the addition of two articles identified through the review of the lists of references of eligible articles, we screened the titles of abstracts of 287 articles, and excluded 227 which appeared not to be relevant. We then reviewed the full text of the remaining 60 articles, and excluded 32 (17 commentaries, reviews or meta-analysis; three letters to the editor without original results, six reports of studies of ovarian cancer without results on talc use, and six articles whose results were superseded by subsequent publications). The remaining 28 articles, comprising three cohort studies, 24 case-control studies, and one pooled analysis of eight of the 24 case-control studies, were included in the review and meta-analysis.



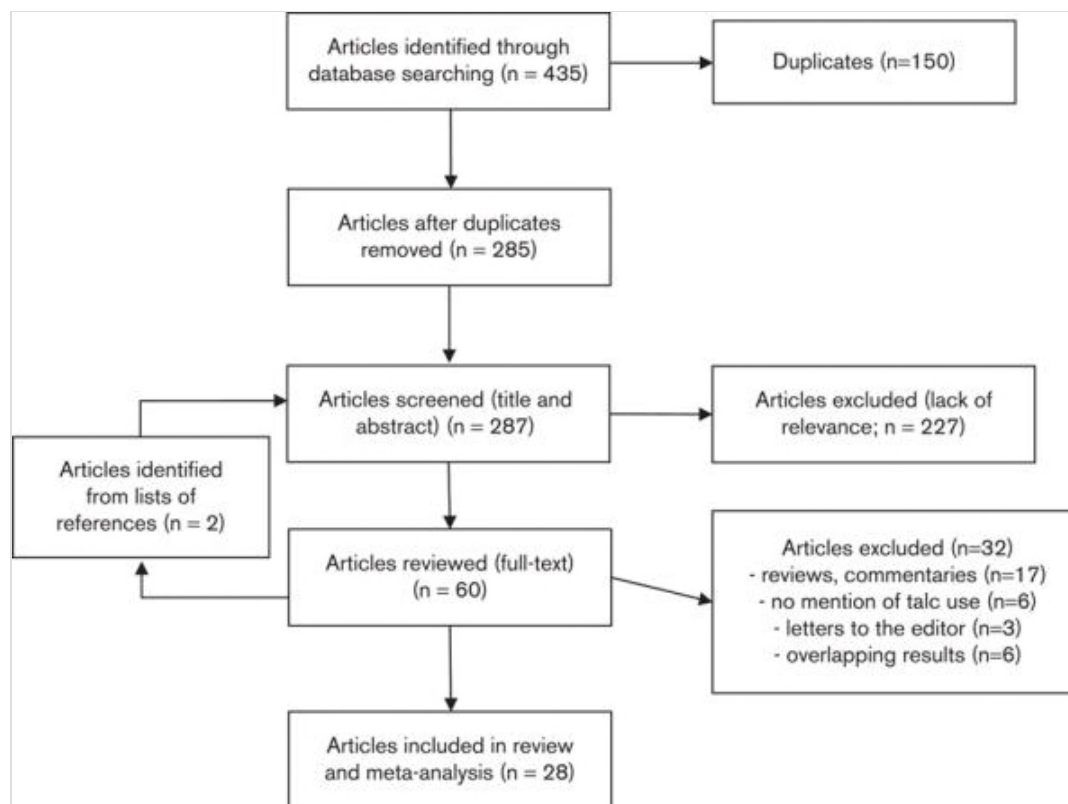


Fig. 1. Flow chart for the selection of studies to include in the meta-analysis.

Table 1 shows selected characteristics of the 28 articles included in the review, which provided the 27 risk estimates included in the meta-analysis [the pooled analysis (Terry et al., 2013) did not provide an independent risk estimate]. For three of the case-control studies included in the pooled analysis (Goodman et al., 2008; Moorman et al., 2009; Lo-Ciganic et al., 2012) results on genital talc use had not been reported in the original publications and were abstracted from the pooled analysis (Terry et al., 2013). Twenty studies were conducted in the USA, two in Australia, two in Canada, one in Great Britain, one in China, and one in Greece. Potential confounding factors including age, parity, history of tubal ligation or hysterectomy, and use of oral contraceptive were adjusted for in most studies, although there were differences in the specific adjustments across studies. Six of the 24 case-control studies were hospital-based with the remainder being population-based.

References	Country	Study type	Age range	N ca/co	Potential confounders	Inclusion in meta-analysis	Overlap between publications
Cramer et al. (1982)	USA	CCC	18-80	215/215	Pa, MS	E, N, D	
Hartge et al. (1983)	USA	HCC	NA	135/171	-	E, D	
Whittemore et al. (1985)	USA	HCC	18-74	188/539	Pa, OC	E, N, D, Du, F	
Booth et al. (1989)	UK	HCC	20-64	235/451	SES	E, F	
Hallow and Weiss (1989)	USA	CCC	20-79	116/158	Pa, OC	E, N, D	
Chen et al. (1992)	China	CCC	NA	113/224	Pa, Ed	E	
Hallow et al. (1992)	USA	CCC	18-78	235/239	Pa, Ed, MS, BMI	E, H, B, F, Du, T, N, D	
Rosenblatt et al. (1992)	USA	HCC	All	77/46	-	E, N, D	
Tzonou et al. (1993)	Greece	HCC	<75	189/200	Pa, Ed, BMI, AMe, MS, AFB, Tob, Cof, Alc, Med, HD	E, N, D	
Purdie et al. (1995)	Australia	CCC	18-79	824/860	Pa	E	
Chang and Risch (1997)	Canada	CCC	35-79	450/584	OC, NP, BF, TL, Hys, FH	Du, T, N	Included in Terry et al. (2013)
Cook et al. (1997)	USA	CCC	20-79	313/422	-	E, H, Du, N, D	
Godard et al. (1998)	Canada	CCC	20-84	170/170	-	E	
Wong et al. (1999)	USA	HCC	NA	499/755	Pa, OC, Tob, FH, AMe, MS, Inc, Ed, TL, Hys	E, Du, N	
Ness et al. (2000)	USA	CCC	20-69	767/1367	NP, FH, OC, TL, Hys, BF	E, Du, N, D	
Mita et al. (2004)	USA	CCC	18+	256/1122	OC, BF	E, H, B, F, Du, T	
Goodman et al. (2008)	USA	CCC	18+	367/802	NA	-	Included in Terry et al. (2013)
Moorman et al. (2009)	Australia	CCC	18-79	1579/1509	Pa, Ed, OC	Du	Included in Terry et al. (2013)
Lo-Ciganic et al. (2012)	USA	CCC	20-74	1086/1057	-	-	Included in Terry et al. (2013)
Gates et al. (2010)	USA	Cohort	30-55	721/-	Pa, BMI, PA, Tob, FH, BF, OC, TL, Hys, Amp, HRT	E, H, P, N <sup>a</sup>	
Rosenblatt et al. (2011)	USA	CCC	35-74	812/1313	NP, OC	Du, T, N, D	Included in Terry et al. (2013)
Lo-Ciganic et al. (2012)	USA	CCC	25+	902/1802	NA	-	Included in Terry et al. (2013)
Terry et al. (2013)	USA, Canada, Australia	CCC	-	-	Pa, OC, TL, BMI	E, H, B	Pooled data from Chang and Risch (1997), Goodman et al. (2008), Moorman et al. (2009), Rosenblatt et al. (2011), Lo-Ciganic et al. (2012), Merritt et al. (2008)
Houghton et al. (2014)	USA	Cohort	50-79	429/-	Pa, OC, HRT, FH, ALB, BMI, Tob, TL	E, H, N, D, Du	
Wu et al. (2015)	USA	CCC	18-74	1701/2391	MS, AMe, HRT, BMI, Inc, Ed, NP, OC, TL, End, FH	E, T <sup>b</sup>	
Cramer et al. (2016)	USA	CCC	18-80	2041/2100	-	E, H, B, F, Du, D	
Gonzalez et al. (2016)	USA, Puerto Rico	Cohort	35-74	164/-	BMI, OC, MS, TL, Hys	E	
Schildkraut et al. (2016)	USA	CCC	20-79	584/745	Pa, Ed, OC, BMI, TL, FH	E, H, Du, F	

N ca/co, number of cases and controls (only cases for cohort studies); AFB, age at first birth; ALB, age at last birth; AMe, age at menarche; AMp, age at menopause; B, tumor behavior; BF, breast feeding; CCC, community-based case-control study; D, diaphragm use; Du, duration of use; E, ever use; Ed, education; F, frequency of use; FH, family history of breast and ovarian cancer; H, histologic type; HCC, hospital-based case-control study; HD, hair dye use; HRT, hormone replacement therapy; Hys, hysterectomy; Inc, income; Med, use of medications; MS, menopausal status; N, sanitary napkin use; NA, not available; NP, number of pregnancies; OC, oral contraceptive use; Pa, parity; SES, socioeconomic status; T, timing of use; TL, tubal ligation.  
<sup>a</sup>Results abstracted from Gertig et al. (2000).  
<sup>b</sup>Results abstracted from Wu et al. (2009).

Table 1 Selected characteristics of the studies included in the meta-analysis

The results of the meta-analysis are reported in Table 2. We used the results reported in the meta-analysis by Terry et al. (2013) for six of the original eight studies (Chang and Risch, 1997; Goodman et al., 2008; Merritt et al., 2008; Moorman et al., 2009; Rosenblatt et al., 2011; Lo-Ciganic et al., 2012), while for the remaining two studies (Cramer et al., 1999; Pike et al., 2004) we used the more extensive results reported in subsequent publications (Wu et al., 2015; Cramer et al., 2016).

	Number of risk estimates	RR	95% CI	p-het
Overall	27	1.22	1.13–1.30	0.02
Study design				
Cohort studies	3	1.02	0.85–1.20	0.2
Case–control studies	24	1.26	1.17–1.35	0.08
Hospital-based case–control studies	6	1.34	1.16–1.51	0.8
Community-based case–control studies	18	1.24	1.13–1.35	0.03
Histology				
Serous carcinoma	13	1.24	1.15–1.34	0.4
Mucinous carcinoma	12	0.96	0.73–1.18	0.8
Endometrial carcinoma	12	1.15	0.91–1.39	0.1
Clear cell carcinoma	8	0.98	0.72–1.23	0.8
Behavior				
Invasive	9	1.20	1.08–1.31	0.2
Borderline	9	1.27	1.09–1.44	0.9
Period of exposure <sup>a</sup>				
Early	5	1.18	0.99–1.37	0.2
Late	5	1.31	1.03–1.61	0.2
Specific sources of talc exposure				
Sanitary napkin	12	1.00	0.84–1.16	0.5
Diaphragm	11	0.75	0.63–0.88	0.8

CI, confidence interval; p-het, *P*-value of test for interstudy heterogeneity; RR, relative risk.

<sup>a</sup>Cut-points between periods vary across studies but in general refer to 1970 or 1980.

Table 2 Ever use of genital talc – results of meta-analysis

The meta-analysis of all 27 risk estimates for ever use of genital talc yielded a summary RR of 1.22 (95% CI: 1.13–1.30). The forest plot of these results is shown in Fig. 2. When the meta-analysis was stratified according to study design, an association with ever genital talc use was detected in case–control studies (RR: 1.26; 95% CI: 1.17–1.35), but not in cohort studies (RR: 1.02; 95% CI: 0.85–1.20). The *P*-value of the test for heterogeneity of results according to study design was 0.007.

Furthermore, hospital-based case–control studies resulted in a higher summary RR than community-based case–control studies (*P*=0.3, for heterogeneity between the two groups of case–control studies).

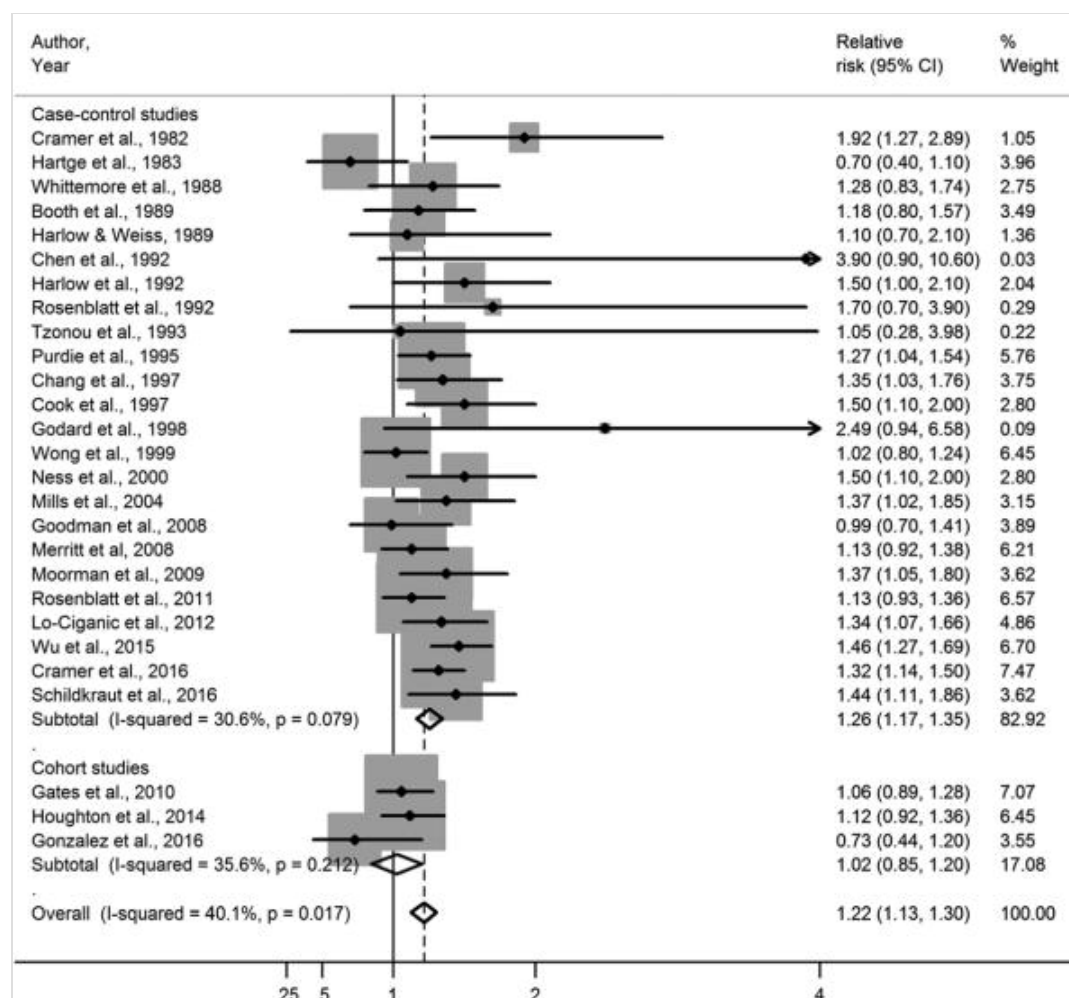


Fig. 2. Forest plot of results on ever use of genital talc and risk of ovarian cancer. CI, confidence interval.

The meta-analysis stratified by tumor behavior did not reveal a difference between results for borderline (RR: 1.27; 95% CI: 1.09–1.44) and invasive ovarian cancer (RR: 1.20; 95% CI: 1.08–1.31). The analysis stratified by histology, however, identified an association between ever genital use of talc and serous carcinoma (RR: 1.24; 95% CI: 1.15–1.34, on the basis of 13 case-control studies and no cohort studies). No significant associations were detected for endometrial (RR: 1.15; 95% CI: 0.91–1.39), mucinous (RR: 0.96; 95% CI: 0.73–1.18) or clear cell (RR: 0.98; 95% CI: 0.72–1.23) carcinomas. The *P*-value of the test of heterogeneity between histologic types was 0.04. Only two cohort studies reported histology-specific results, showing neither a difference between types nor stronger association for serous carcinoma (results not shown in detail). Three of the studies (Mills et al., 2004; Rosenblatt et al., 2011; Cramer et al., 2016) reported results for serous carcinoma stratified by tumor behavior: they did not suggest any difference (RR=1.39, for borderline serous carcinoma; 95% CI: 1.04–1.74; RR: 1.32, for invasive serous carcinoma; 95% CI: 0.97–1.67; *P*<sub>heterogeneity</sub>=0.5).

Use of talcum powder in the 'early' period showed weakly increased risk of ovarian cancer (RR: 1.18; 95% CI: 0.99–1.37), whereas the RR for use in the 'late' period was slightly higher but less precisely estimated (RR: 1.31; 95% CI: 1.03–1.61). The *P*-value of the test for heterogeneity between groups of studies was 0.37.

Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR: 1.00; 95% CI: 0.84–1.16; and RR: 0.75; 95% CI: 0.63–0.88, respectively).

We conducted additional analyses after stratifying the studies according to whether the results were adjusted for key potential confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/education, BMI; see Table 1 for details), but found no evidence of heterogeneity (results not shown in detail).

The results of the analysis by duration and frequency of genital talc use are reported in Table 3. A 10-year increase in genital talc use was associated with a RR of 1.16 (95% CI 1.07-1.26; 12 studies), whereas the RR for an increase of one application per week was 1.05 (95% CI 1.04-1.07; 7 studies).

	Number of risk estimates	RR	95% CI
Duration (10 years)	12	1.16	1.07–1.26
Frequency (1 time/week)	7	1.05	1.04–1.07

CI, confidence interval; p-het, RR, relative risk.

Table 3 Duration and frequency of use of genital talc – results of meta-analysis

The funnel plot of the results of ever genital talc use is shown in Fig. 3. Visual inspection of the plot suggests no serious publication bias: this conclusion is supported by the result of the Egger test ( $P=0.7$ ). The results of the cumulative meta-analysis (Fig. 4) suggest that after the publication of a few initial studies with inconsistent results, the summary RR stabilized with values in the range of 1.20–1.25.

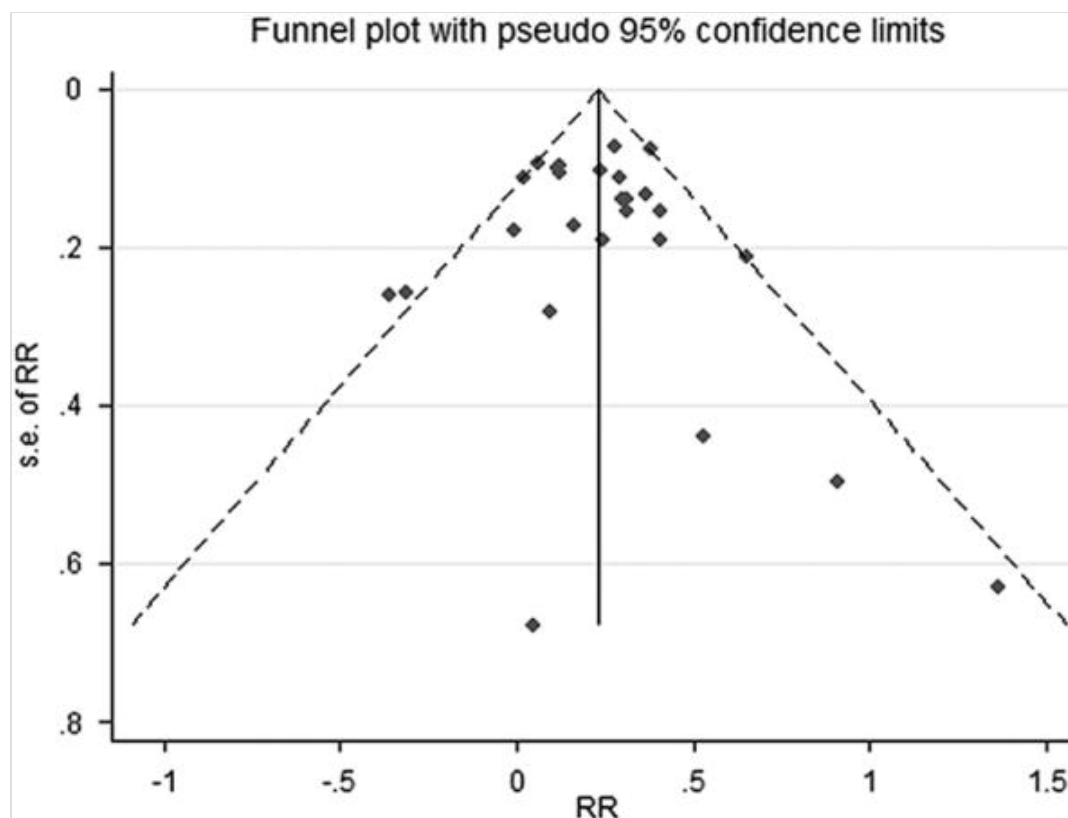


Fig. 3. Funnel plot of results on ever use of genital talc and risk of ovarian cancer. RR, relative risk.

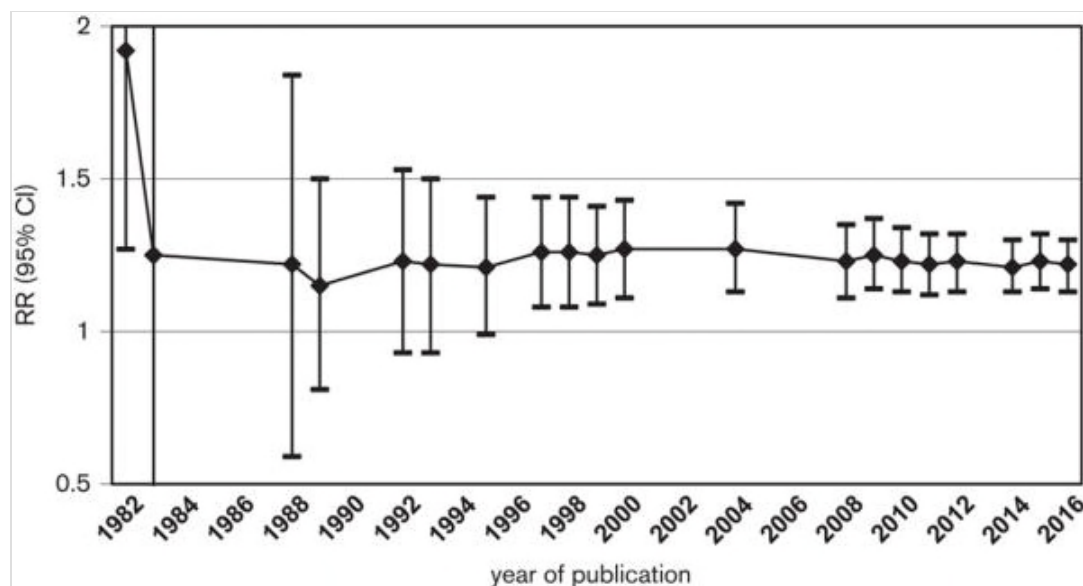


Fig. 4. Cumulative meta-analysis of results on ever use of genital talc and risk of ovarian cancer. CI, confidence interval; RR, relative risk.

## Discussion

Ovarian cancer, unless diagnosed and treated early, remains a highly lethal disease and the identification of modifiable risk factors is an important component of the strategy for its control. The primary aim of this meta-analysis was to determine whether talcum powder use in the female genital area is a potential risk factor for ovarian cancer. Previous meta-analyses ([Huncharek et al., 2003](#); [Langseth et al., 2008](#)) were only on the basis of a fraction of currently available studies, and had limited ability to explore potential sources of heterogeneity in results.

This meta-analysis suggests that genital powder use is associated with a small increased risk of developing ovarian cancer; however, this positive association appears to be limited to the serous histologic type, and to case-control studies. This estimate is somewhat lower than that of previous meta-analyses ([Huncharek et al., 2003](#); [Langseth et al., 2008](#)): in our cumulative meta-analysis we confirmed the trend toward lower overall risk estimates as more evidence accumulated.

An important feature of the present meta-analysis is the inclusion of several cohort studies, which enabled an analysis stratified by study design. This analysis provided evidence of heterogeneity of results between the two groups of studies, with an association generally detected in case-control studies but not in cohort studies. It should be noted that the cohort studies included in the meta-analysis comprised a total of 429 cases of ovarian cases exposed to genital talc and 943 unexposed cases: the statistical power of the meta-analysis of these cohort studies to detect a RR of 1.25, similar to the result of the meta-analysis of case-control studies, was 0.99. Thus, low power of cohort studies cannot be invoked as explanation of the heterogeneity of results.

The fact that the association between genital talc use and risk of ovarian cancer is present in case-control, but not in cohort studies, can be attributed to bias in the former type of studies ([Kopce and Esdaile, 1990](#); [Rothman et al., 2008](#)). Selection bias might have played a role in the results of some of the case-control studies (e.g. those with low response rate, or those hospital-based, which resulted in a nonsignificantly higher summary risk estimate than community-based studies); in addition, information bias from retrospective self-report of talc use is a possible explanation for the association detected in case-control studies. In particular, some of the most recent case-control studies ([Cramer et al., 2016](#); [Schildkraut et al., 2016](#)) have reported particularly strong associations ( $RR > 1.4$ ) for ever use of talc. These results may have occurred at least in part because of participants' knowledge about the latest controversies about talc use and ovarian cancer risk spread by the media ([Muscat and Huncharek, 2008](#)).



The results of the analysis by histologic type of ovarian cancer pointed toward an association with serous carcinoma, but not with the other main types (i.e. endometrial, mucinous, and clear cell carcinoma). Several studies have suggested heterogeneity in risk factors of different histologic types, which are characterized by distinctive molecular and genetic profiles (Kurian et al., 2005; Gates et al., 2010; Gilks, 2010). However, no results are available on whether the association between asbestos exposure and ovarian cancer risk varies by histologic type (Camargo et al., 2011; Reid et al., 2011). The finding that the association between genital talc use and ovarian cancer may vary by histologic type detracts from the hypothesis of report bias as an explanation of the findings of case-control studies, as this type of bias would likely operate for all histologic types of the disease. Caution should however be warranted in the interpretation of these findings, as the test for heterogeneity between groups was of borderline statistical significance, and the evidence for heterogeneity derives only from case-control studies.

The presence or absence of a dose-response is an important aspect to consider in assessing the plausibility of the causal nature of an association observed in a meta-analysis. The number of studies included in the analysis of duration and frequency of genital talc use was not very large, and the modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding, and analyses based on larger datasets would be required is a potentially important and novel contribution of this meta-analysis.

We aimed at analyzing the results on genital use of talc according to time-periods; this analysis was limited by different cut-points used by various authors to define time intervals of exposure. In general, however, we were able to distinguish an 'early' and a 'late' period, with the limit between the two running between 1970 and 1980, and we found a statistically significant association only for 'late' use. This result goes against the hypothesis that a stronger association (if any) would be seen among those more likely to have used talcum powders in a time period in which contamination with asbestos fibers was possible (Rohl et al., 1976).

Our study suffers from limitations common to meta-analyses of observational studies: neither the definition of the exposure of interest (genital talc use) nor the strategy for adjustment for potential confounders were fully consistent across studies. Also, there were limitations not specific to our study, including the self-reported information on the main exposure of interest, with no external validation data, the predominance of retrospective case-control studies, and the small number of studies providing results by histologic type or quantitative measures of genital talc use. It is difficult to assess the combined effect of the potential sources of bias, as they might have operated in different directions on the estimate of the association between talc use and ovarian cancer. The stratified analyses we conducted did not point toward the presence of residual confounding (i.e. higher risk estimates for unadjusted compared with adjusted results).

The biological basis and plausibility of a possible carcinogenic effect of talc on the ovaries is still not understood and remains questionable. The similarity of physicochemical characteristics of talc and asbestos has been proposed to explain a carcinogenic effect of the former (Cramer et al., 1982). However, although both talc and various forms of asbestos minerals belong to the family of silicates, they are morphologically distinct. It is the fibrous form of asbestos which determines its carcinogenic potential (Stanton et al., 1981; Huncharek, 1986; Mossman and Gee, 1989). Talc is not fibrous or crystalline (International Agency for Research on Cancer (IARC), 2010), and in-vitro studies have shown that talc is not genotoxic (Wehner, 1994). This is supported by the evidence that exposure to talc not contaminated with asbestiform fibers is not associated with increased risk of lung cancer or mesothelioma in occupational cohorts (International Agency for Research on Cancer (IARC), 2010). The occupational cohorts supporting this conclusion comprise mostly men, and therefore provide no evidence in favor or against the hypothesis of a role of occupational talc exposure as an ovarian carcinogen, but the likelihood that talc could selectively cause ovarian cancer but not lung cancer or mesothelioma at high concentrations in talc miners and millers appears to be low. Furthermore, there is no evidence that occupational exposure to talc, for example, in the pulp and paper industry, entails an increased risk of ovarian cancer (Langseth and Kjaerheim, 2004).

In conclusion, our meta-analysis identified a small but statistically significant association between genital talc use and risk of ovarian cancer; however, this association was limited to the serous histologic type, and to case-control studies. The results by histologic type might argue for specificity of the association, in the absence, however, of a biologic rationale for an effect on serous carcinoma compared with other types. Several aspects of our results, including the heterogeneity of results between case-control and cohort studies, however, do not support a causal interpretation of the association.

## Acknowledgements

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#### Conflicts of interest

There are no conflicts of interest.

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Keywords: meta-analysis; ovarian cancer; talc

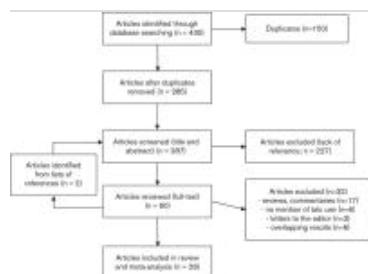
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## IMAGE GALLERY

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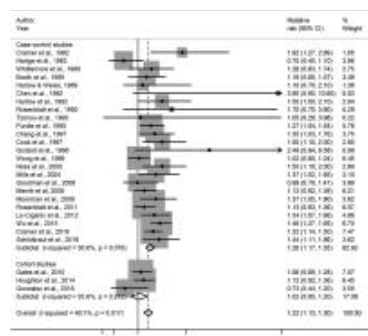
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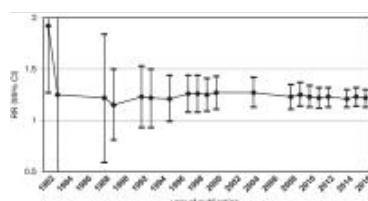
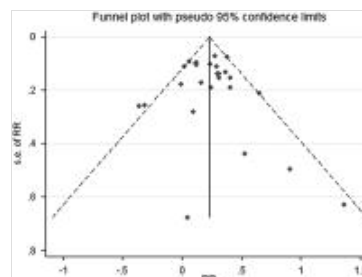
Parameter	Unit	Value	Uncertainty	Reference
Mean value of $\mu$	mm	10.0	0.1	[1]
Standard deviation of $\mu$	mm	0.5	0.05	[1]
Mean value of $\sigma$	mm	1.0	0.1	[1]
Standard deviation of $\sigma$	mm	0.2	0.02	[1]
Mean value of $\tau$	mm	1.5	0.1	[1]
Standard deviation of $\tau$	mm	0.3	0.03	[1]
Mean value of $\delta$	mm	2.0	0.2	[1]
Standard deviation of $\delta$	mm	0.4	0.04	[1]
Mean value of $\epsilon$	mm	2.5	0.2	[1]
Standard deviation of $\epsilon$	mm	0.5	0.05	[1]
Mean value of $\eta$	mm	3.0	0.3	[1]
Standard deviation of $\eta$	mm	0.6	0.06	[1]
Mean value of $\theta$	mm	3.5	0.3	[1]
Standard deviation of $\theta$	mm	0.7	0.07	[1]
Mean value of $\phi$	mm	4.0	0.4	[1]
Standard deviation of $\phi$	mm	0.8	0.08	[1]
Mean value of $\psi$	mm	4.5	0.4	[1]
Standard deviation of $\psi$	mm	0.9	0.09	[1]
Mean value of $\chi$	mm	5.0	0.5	[1]
Standard deviation of $\chi$	mm	1.0	0.1	[1]
Mean value of $\lambda$	mm	5.5	0.5	[1]
Standard deviation of $\lambda$	mm	1.1	0.11	[1]
Mean value of $\kappa$	mm	6.0	0.6	[1]
Standard deviation of $\kappa$	mm	1.2	0.12	[1]
Mean value of $\iota$	mm	6.5	0.6	[1]
Standard deviation of $\iota$	mm	1.3	0.13	[1]
Mean value of $\upsilon$	mm	7.0	0.7	[1]
Standard deviation of $\upsilon$	mm	1.4	0.14	[1]
Mean value of $\omega$	mm	7.5	0.7	[1]
Standard deviation of $\omega$	mm	1.5	0.15	[1]
Mean value of $\nu$	mm	8.0	0.8	[1]
Standard deviation of $\nu$	mm	1.6	0.16	[1]
Mean value of $\xi$	mm	8.5	0.8	[1]
Standard deviation of $\xi$	mm	1.7	0.17	[1]
Mean value of $\zeta$	mm	9.0	0.9	[1]
Standard deviation of $\zeta$	mm	1.8	0.18	[1]
Mean value of $\eta$	mm	9.5	0.9	[1]
Standard deviation of $\eta$	mm	1.9	0.19	[1]
Mean value of $\theta$	mm	10.0	1.0	[1]
Standard deviation of $\theta$	mm	2.0	0.2	[1]

	Number of risk estimates	RR	95% CI	p-value
Overall	27	1.22	1.13-1.30	0.001
Study design				
Cohort studies	3	1.02	0.88-1.20	0.81
Case-control studies	24	1.20	1.17-1.23	0.001
Hospital-based case-control studies	6	1.34	1.16-1.51	0.001
Community-based case-control studies	18	1.24	1.13-1.35	0.001
Histology				
Squamous carcinoma	13	1.24	1.15-1.34	0.001
Mucinous carcinoma	12	0.94	0.73-1.18	0.61
Endometrial carcinoma	12	1.15	0.91-1.39	0.22
Clear cell carcinoma	0	0.98	0.72-1.23	0.91
Behavior				
Invasive	9	1.20	1.06-1.31	0.001
Borderline	9	1.27	1.09-1.44	0.001
Period of exposure <sup>a</sup>				
Early	5	1.18	0.99-1.37	0.05
Late	5	1.31	1.03-1.61	0.02
Specific sources of fat exposure				
Sanitary napier	12	1.00	0.84-1.16	0.95
Diaphragm	11	0.75	0.63-0.88	0.001



	Number of risk estimates	RR	95% CI
Duration (10 years)	12	1.16	1.07-1.26
Frequency (1 time/week)	7	1.05	1.04-1.07

CI, confidence interval; RR, relative risk.



# Exhibit 62

# Perineal Talc Use and Ovarian Cancer

## A Systematic Review and Meta-Analysis

Ross Penninkilampi, and Guy D. Eslick

**Background:** It has been posited that there is an association between perineal talc use and the incidence of ovarian cancer. To date, this has only been explored in observational studies.

**Objectives:** To perform a meta-analysis to evaluate the association between perineal talc use and risk of ovarian cancer.

**Methods:** Studies were identified using six electronic databases. Observational studies involving at least 50 cases of ovarian cancer were eligible for inclusion. We analyzed the association between ovarian cancer, including specific types, and any perineal talc use, long-term (>10 years) use, total lifetime applications, and use on diaphragms or sanitary napkins. A subgroup analysis was performed, stratifying by study design and population.

**Results:** We identified 24 case-control (13,421 cases) and three cohort studies (890 cases, 181,860 person-years). Any perineal talc use was associated with increased risk of ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). More than 3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) were slightly more associated with ovarian cancer than <3600 (OR = 1.32; 95% CI = 1.15, 1.50). An association with ever use of talc was found in case-control studies (OR = 1.35; 95% CI = 1.27, 1.43), but not cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). However, cohort studies found an association between talc use and invasive serous type ovarian cancer (OR = 1.25; 95% CI = 1.01, 1.55). We found an increased risk of serous and endometrioid, but not mucinous or clear cell subtypes.

**Conclusions:** In general, there is a consistent association between perineal talc use and ovarian cancer. Some variation in the magnitude of the effect was found when considering study design and ovarian cancer subtype.

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This manuscript is original, has not been previously published in whole or in part, and is not under consideration for publication elsewhere. Neither animals nor human subjects were used in this research.

All authors have read the manuscript, agree that the work is ready for submission, and accept the contents of the manuscript.

The authors report no conflicts of interest.

**SDC** Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article ([www.epidem.com](http://www.epidem.com)).

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Ovarian cancer is the gynecologic cancer associated with the highest mortality in the United States, in 2012 being the fifth highest cause of cancer death in women with 14,404 deaths in that country.<sup>1</sup> The National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) predicts that in the United States, in 2016, there will be 22,280 incidences of newly diagnosed ovarian cancer, and 14,240 deaths caused by ovarian cancer based on age-adjusted data from 2009 to 2013.<sup>2</sup> The 5-year survival statistics for ovarian cancer are poor, largely because patients usually present with advanced disease, which is less amenable to curative therapy.<sup>3</sup> SEER estimates that only 15% of patients present with disease localized to the ovary, which contributes to a 5-year survival of 46.2%.<sup>2</sup> It is imperative to develop public health programs, which either reduce the incidence of ovarian cancer or detect it at an earlier stage, to reduce the burden of this disease.

Routine pelvic examinations, transvaginal ultrasonography, and tumor markers have been trialed as potential screening tools for ovarian cancer, but are limited in their usefulness. The cancer marker cancer antigen 125 (CA-125, also known as mucin 16) has been found to be elevated in 80% of all ovarian carcinomas, but this falls to 50% in women in which the cancer is localized only to the ovary, where it is most amenable to treatment.<sup>4</sup> As CA-125 has a low sensitivity and limited specificity, it is not recommended as a screening test for women without clinical symptoms.<sup>5</sup> Ultrasound has a reasonable sensitivity but poor specificity and positive predictive value, particularly as it is poor at distinguishing between benign and malignant masses.<sup>6</sup> While the search for an effective screening regimen for ovarian cancer continues, the importance of primary prevention becomes paramount.

Talcum powder is made of talc, a hydrated magnesium silicate, and is used to absorb moisture on the body. Some women choose to dust talc on the perineum, or apply it to diaphragms or sanitary napkins, to reduce friction, keep the skin dry, reduce odor, and prevent rashes. The potential association between perineal talc use and ovarian cancer has been discussed for decades. The first investigation of this association was performed by Cramer et al<sup>7</sup> in 1982, when the investigators found a relative risk of 1.92 (95% CI = 1.27, 2.89) for ovarian cancer when women either dusted the perineum with talc powder or used it on sanitary napkins. Since this time, there has been substantial interest in and research into this association.

In the present context, the association between talc use and ovarian cancer takes on considerable relevance, as the pharmaceutical and consumer products company Johnson & Johnson has recently had damages levied to the total of US\$717 million against them in five law suits. In these cases, juries decided that the use of talcum powder caused or contributed to the development of the plaintiff's ovarian cancer. The evidence for the association between perineal talc use and ovarian cancer is based on the body of knowledge from observational studies, and most of these have been retrospective case-control studies prone to recall bias. Hence, while perineal talc use has not been shown to be safe, in a similar regard, a certain causal link between talc use and ovarian cancer has not yet been established.<sup>8,9</sup>

In 2013, a pooled analysis was performed for eight population-based case-control studies, and found a modest increased risk (OR = 1.24) of ovarian carcinoma associated with perineal talc use.<sup>10</sup> In 2007, a meta-analysis was performed of nine observational studies; however, this study only examined the use of talc on contraceptive diaphragms.<sup>11</sup> The overall finding of this meta-analysis was that the use of talc on contraceptive diaphragms was not associated with ovarian cancer. Meta-analyses have been performed on this subject before; however, the most recent was in 2008,<sup>9</sup> and since this time, the results of a number of large case-control studies and two cohort studies<sup>12,13</sup> have been published. Hence, there is a need to update the literature, particularly considering pending litigation against Johnson & Johnson by other claimants, and Johnson & Johnson's potential plans to appeal the previous decisions. Furthermore, producers of talcum powder products continue to sell these products without any warning labels regarding perineal use and potential associations with ovarian cancer. Hence, there is a need for clarification, to allow women to be adequately informed of the risk of use of these products, possibly preventing future harm.

This paper aims to review the literature and provide an overall risk estimate for the association between perineal talc use and ovarian carcinoma. We will also perform subgroup analyses by the method of talc application, the duration of talc use, the total number of perineal talc applications, and the type of ovarian cancer developed to further elucidate the relationship between talc use and ovarian carcinoma.

## METHODS

### Study Protocol

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.<sup>14</sup> R.P. performed a systematic search of the databases MEDLINE (from 1950), PubMed (from 1946), Embase (from 1949), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), LILACS, and the Cochrane Central Register of Controlled Trials through 22 August 2017 to identify relevant articles. The search used the terms ("talc" OR "talcum

powder") AND ("ovarian cancer" OR "ovarian carcinoma"), which were searched as text word and as exploded medical subject headings where possible. We also searched the reference lists of relevant articles for appropriate studies. No language restrictions were used in either the search or study selection. We did not search for unpublished literature.

### Study Selection

We included studies that met the following inclusion criteria: (1) the study investigated the perineal use of talc in relation to risk of development of ovarian cancer; (2) the study reported adverse events as an odds ratio (OR), or the data were presented such that an OR could be calculated; (3) the 95% confidence interval (CI) was reported, or the data were presented such that the CI could be calculated; and (4) the study involved a minimum of 50 cases. We excluded studies that did not meet the inclusion criteria.

### Data Extraction

One of us (R.P.) performed data extraction using a standardized data extraction form, collecting information on the publication year, study design, number of cases, number of controls, total sample size, population type, country, mean age, number of adjusted variables, the risk estimates or data used to calculate the risk estimates, CIs or data used to calculate CIs, and the type of ovarian cancer. R.P. assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS); however, no studies were excluded on the basis of NOS score.<sup>15</sup> Authors were not contacted for missing data. Adjusted ratios were extracted in preference to nonadjusted ratios; however, where ratios were not provided, R.P. calculated unadjusted ORs and CIs.

### Statistical Analysis

One of us (G.D.E.) calculated pooled ORs and 95% CIs for the effect of any perineal talc use with all ovarian cancers using a random effects model.<sup>16</sup> Analyses were also performed based on the method of administration (diaphragm, sanitary napkins), duration of use, and type of ovarian cancer developed (all mucinous, mucinous invasive, mucinous borderline, all serous, serous invasive, serous borderline, endometrioid, clear cell). For long-term talc use, we extracted the odds ratio for the group with the longest duration of talc exposure compared with controls, provided that group used talc for a minimum duration of 10 years. For overall lifetime talc applications, groups within each study were divided into either <3600 lifetime applications, equivalent to less than approximately 10 years of daily use, or >3600 applications. Where a group from a study did not completely fit into this dichotomy, we placed it into the category it most closely fit. Details on the categorization of individual groups are available in eTable 1 (<http://links.lww.com/EDE/B261>). Odds ratios were pooled for invasive serous, invasive mucinous, borderline serous, and borderline mucinous tumors individually. However, as many studies reported only all mucinous or all serous in a single

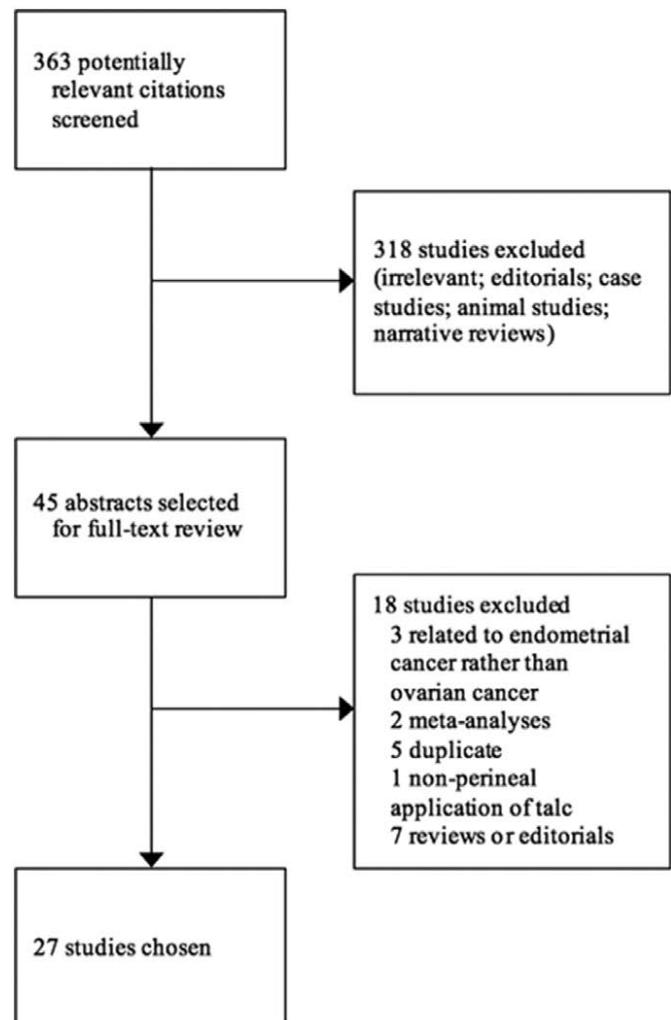
group, we also ran analyses for risk associated with all mucinous and all serous tumors. Where a study reported separately as borderline and serous, both odds ratios were included separately in the meta-analysis, to ensure all available data were considered.

We tested heterogeneity with Cochran's  $Q$  statistic, with  $P < 0.10$  indicating heterogeneity, and quantified the degree of heterogeneity using the  $I^2$  statistic, which represents the percentage of the total variability across studies which is due to heterogeneity.  $I^2$  values of 25%, 50%, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively.<sup>17</sup> We quantified publication bias using the Egger's regression model,<sup>18</sup> with the effect of bias assessed using the fail-safe number method. The fail-safe number was the number of studies that we would need to have missed for our observed result to be nullified to statistical nonsignificance at the  $P < 0.05$  level. Publication bias is generally regarded as a concern if the fail-safe number is less than  $5n + 10$ , with  $n$  being the number of studies included in the meta-analysis.<sup>19</sup> All analyses were performed with Comprehensive Meta-analysis (version 3.0; Biostat, Englewood, NJ; 2014).

## RESULTS

### Study Characteristics

We performed a broad literature search of electronic databases, identifying 363 citations for review (Figure 1). Initially, 318 studies were discarded, with many being narrative reviews, duplicates, animal studies, opinion pieces, editorials, or otherwise irrelevant. Forty-five citations were selected for full-text review. Of these, three were excluded due to being associated with endometrial rather than ovarian cancer, two were meta-analyses, five were duplications of data from the same study, one involved non-perineal application of talc, and seven were otherwise irrelevant. No studies were excluded for failing to report an odds ratio or for not providing the necessary raw data from which an odds ratio could be provided. Some studies provided only the raw data, i.e., the number of cases and controls with and without perineal talc use. This allowed an unadjusted odds ratio to be calculated, which was then included in the analysis. Overall, 27 studies were selected. Note that Wu et al<sup>33</sup> (2015) include results from Wu et al<sup>36</sup> (2009); however, only Wu et al<sup>36</sup> (2009) reported on non-perineal talc use, total lifetime applications, and long-term talc use. Hence data were extracted from Wu et al<sup>33</sup> (2015) for the "any perineal use" outcome, and from Wu et al<sup>36</sup> (2009) for the three other outcomes previously mentioned. Hence, while 27 studies were included in the analysis, only 26 were included in the any perineal use analysis. Three studies were cohort studies, including 890 cases and 181,860 person-years.<sup>12,13,20</sup> The remaining 26 studies were case-control studies, with a total of 13,421 cases and 19,314 controls. The case-control studies are described in eTable 1 (<http://links.lww.com/EDE/B261>), while the cohort studies are described in eTable 2 (<http://links.lww.com/EDE/B261>).



**FIGURE 1.** PRISMA flowchart for literature search and study selection.

[lww.com/EDE/B261](http://links.lww.com/EDE/B261)). In total, studies involving 14,311 cases of ovarian cancer were included in this review.

The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which involves separate assessment tools for both case-control and cohort studies.<sup>15</sup> The highest score awarded was 8/10, and the lowest was 5/10. The mean score was 7.0. Almost all studies lost points because the exposure to talc was ascertained through self-report rather than an independently verified source, and because the interviewer was not blinded to cases and controls. Many studies also failed to specifically describe that their chosen controls did not have a personal history of previous ovarian cancer. It may be the case that this was done, but not reported in the study methods. Generally, case ascertainment and matching controls based on age and other factors, often geographical location or ethnicity, were well performed in the reviewed studies. The breakdown of individual study scores is included in Tables 1 and 2. Overall, the quality of studies included in



**TABLE 1.** Summary of Pooled Effect Sizes for Examined Outcome Variables

	No. Studies	Effect Size	Heterogeneity		Publication Bias	
		OR (95% CI)	I <sup>2</sup>	P	P	
Method of talc use						
Any perineal	26	1.31 (1.24, 1.39)	10.52	0.31	0.09	
Any non-perineal	5	1.24 (1.01, 1.51)	66.84	0.02	0.86	
Diaphragm	8	0.84 (0.68, 1.05)	14.76	0.31	0.64	
Sanitary napkins	12	1.15 (0.94, 1.41)	43.82	0.05	0.17	
Length of talc use						
Long-term use (>10 years)	12	1.25 (1.10, 1.43)	45.11	0.04	0.31	
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0.20	
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0.40	
Type of ovarian cancer						
All serous	10	1.32 (1.22, 1.43)	0.00	0.75	0.44	
Serous invasive	5	1.32 (1.13, 1.54)	25.10	0.25	0.75	
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0.83	
All mucinous	9	1.12 (0.94, 1.33)	5.79	0.39	0.79	
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	NA <sup>a</sup>	
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.22	0.96	
Endometrioid	8	1.35 (1.14, 1.60)	0.00	0.61	0.78	
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0.22	

<sup>a</sup>NA = not applicable; no publication bias ... result available when there are fewer than three studies in the analysis.

this review was reasonably high. No studies were excluded from the review based on NOS score.

All studies reported at least an odds ratio for any perineal use of talc and its association with ovarian cancer. As previously described, Wu et al<sup>36</sup> (2009) was not included in this analysis to prevent duplication of data. Five studies reported on only non-perineal exposure. Additionally, eight studies provided data for use of talc on a diaphragm, and 12 for sanitary napkins. Twelve studies provided an odds ratio for long-term talc use and its association with ovarian cancer; however, the chosen threshold for long term was variable, from more than 10 years to more than 37.4 years. Five studies reported on the total number of talc applications. It was frequently necessary to report different groups from a single study separately to perform the meta-analysis of this outcome, with the groupings being described specifically in eTable 1 (<http://links.lww.com/EDE/B261>). Ten studies reported odds ratios for all serous ovarian cancers, five reported for serous invasive cancers, and three reported for serous borderline cancers. Similarly, nine reported for all mucinous cancers, two for mucinous invasive, and three for mucinous borderline. Eight studies reported odds ratios for endometrioid ovarian cancer, and three reported for clear cell ovarian cancer.

## Quantitative Data Synthesis

The results of the initial pooling of data from all studies are summarized in Table 1. Pooling of data revealed an increased risk of ovarian cancer associated with any perineal use of talc (Figure 2A; OR = 1.31; 95% CI = 1.24, 1.39). Use of talc long term (>10 years) was also associated with an increased ovarian cancer risk (Figure 2B; OR = 1.25; 95% CI = 1.10, 1.43). Both <3600 total lifetime applications (OR = 1.32; 95% CI = 1.15, 1.50) and >3600 lifetime applications (OR = 1.42; 95% CI = 1.25, 1.61) of talc were associated with an increased risk of ovarian cancer, with a slightly higher risk in the group with greater usage. Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer. Any perineal talc use was associated with any serous (Figure 2C; OR = 1.32; 95% CI = 1.22, 1.43), serous invasive (OR = 1.32; 95% CI = 1.13, 1.54), serous borderline (OR = 1.39; 95% CI = 1.09, 1.78), and endometrioid (Figure 2D; OR = 1.35; 95% CI = 1.14, 1.60) subtypes of ovarian cancer, but not the other subtypes.

We performed a subgroup analysis stratifying by study design. It is important to note that there were only three cohort studies, each of which did not report on all the assessed associations. For any perineal talc use, only case-control studies showed an association with ovarian cancer (Figure 2A; OR = 1.35; 95% CI = 1.27, 1.43), while no association was noted for cohort studies (OR = 1.06; 95% CI = 0.90, 1.25). For the other associations assessed, the results are reported in Table 2. In cohort studies, the only association found was between perineal talc use and the incidence of serous invasive cancer subtypes (OR = 1.25; 95% CI = 1.01, 1.55). For borderline serous, borderline mucinous, invasive mucinous, and clear cell ovarian cancer subtypes, no cohort studies provided data for the association and hence the odds ratios reported in eTable 2 (<http://links.lww.com/EDE/B261>) are derived entirely from case-control studies. The only outcome reported in all three cohort studies was any perineal talc use; hence the available data from prospective studies were limited.

A subgroup analysis related to study population setting, i.e., in the hospital or in the general population, was performed for any perineal talc application. Generally, hospital-based studies were older (pre-2000) than the community-based studies. There were seven hospital-based studies, all of which were case-control studies. There were 20 population-based studies, including 17 case-control studies and all three cohort studies. There was no difference between the pooled results for hospital- and population-based studies (OR = 1.22 vs. 1.33), respectively.

There was heterogeneity in the analysis of non-perineal applications of talc ( $I^2 = 66.84$ ;  $P = 0.02$ ). There was no heterogeneity for any of the other outcome measures in either the meta-analysis of all available studies or the subgroup analyses. There was no publication bias in the meta-analysis of any genital talc exposure and ovarian cancer, which included all the studies in the review, except Wu et al<sup>36</sup> (2009) (Figure 3;  $P = 0.09$ ). The result for publication bias for each of the individual analyses is included in Table 1.

**TABLE 2.** Summary of Pooled Effect Sizes in Subgroup Analysis by Study Design

	Case-Control Studies (n = 24)				Cohort Studies (n = 3)			
	No. Studies	Effect Size	Heterogeneity		No. Studies	Effect Size	Heterogeneity	
		OR (95% CI)	I <sup>2</sup>	P		OR (95% CI)	I <sup>2</sup>	P
Method of talc use								
Any perineal use	23	1.35 (1.27, 1.43)	0.00	0.77	3	1.06 (0.90, 1.25)	18.89	0.29
Non-perineal use	5	1.24 (1.01, 1.51)	66.84	0.02	0	NA	NA	NA
Diaphragm	7	0.81 (0.61, 1.08)	21.92	0.26	1	0.92 (0.68, 1.24)	0.00	1.00
Sanitary napkin	10	1.27 (0.98, 1.65)	40.49	0.09	2	0.93 (0.77, 1.13)	0.00	0.77
Length of talc use								
Long-term use	11	1.29 (1.13, 1.47)	40.53	0.08	1	0.98 (0.75, 1.29)	0.00	1.00
<3600 total applications	5	1.32 (1.15, 1.50)	1.83	0.41	0	NA	NA	NA
>3600 total applications	5	1.42 (1.25, 1.61)	12.59	0.33	0	NA	NA	NA
Type of ovarian cancer								
All serous	12	1.34 (1.23, 1.47)	0.00	0.71	2	1.19 (0.97, 1.47)	0.00	0.61
Serous invasive	3	1.36 (1.05, 1.75)	47.96	0.15	2	1.25 (1.01, 1.55)	0.00	0.33
Serous borderline	3	1.39 (1.09, 1.78)	0.00	0.94	0	NA	NA	NA
All mucinous	9	1.15 (0.93, 1.41)	21.03	0.26	2	0.96 (0.61, 1.53)	0.00	0.84
Mucinous invasive	2	1.34 (0.48, 3.79)	69.39	0.07	0	NA	NA	NA
Mucinous borderline	3	1.18 (0.76, 1.81)	34.07	0.21	0	NA	NA	NA
Endometrioid	6	1.39 (1.16, 1.66)	0.00	0.52	2	1.09 (0.66, 1.80)	0.00	0.48
Clear cell	3	1.02 (0.75, 1.39)	0.00	0.78	0	NA	NA	NA

NA = not applicable; no cohort studies reported on the relevant associations.

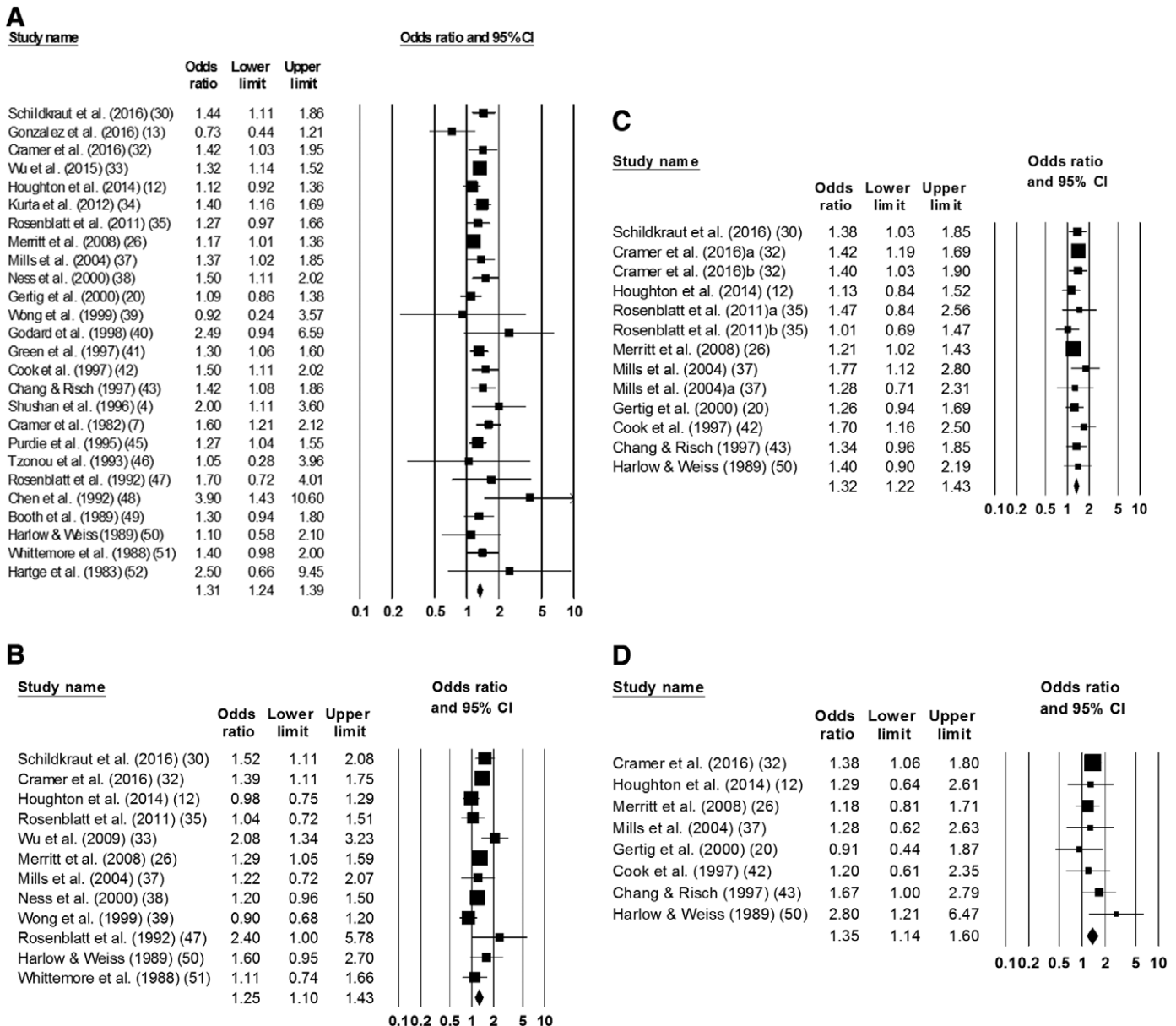
## DISCUSSION

The present meta-analysis reports a positive association between perineal talc use and ovarian cancer, specifically of the serous and endometrioid histologic subtypes. The mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain. It has been previously proposed that talc, as a foreign body, may ascend from the vagina through to the uterine tubes and instigate a chronic inflammatory response, which may predispose to the development of ovarian cancer. It is argued that cellular injury, oxidative stress, and local increase in inflammatory mediators such as cytokines and prostaglandins may be mutagenic and hence promote carcinogenesis.<sup>21</sup> In support of this hypothesis, it has been found that hysterectomy or bilateral tubal ligation, in which ovarian exposure to inflammatory mediators would be significantly curtailed, is associated with a reduced risk of ovarian cancer.<sup>22–24</sup> However, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is not inversely associated with the incidence of ovarian cancer, as may be expected if the etiology was related to chronic inflammation.<sup>25,26</sup> It has also been found that human epithelial ovarian cells have an unusually low expression of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which would reduce their sensitivity to the action of NSAIDs.<sup>27</sup> The potential mechanism by which genital talc is associated with an increased risk of ovarian cancer hence remains unclear.

An important finding of this study is that talc use appears to be associated with increased risk of serous ovarian

cancer, of both invasive and borderline types, and not with mucinous ovarian cancer. Additionally, endometrioid ovarian cancers but not clear cell cancers were significantly associated with perineal talc use. Intriguingly, a meta-analysis examining the effects of tubal ligation of ovarian cancer risk found a reduced risk of the same subtypes of ovarian cancer as mentioned here: serous and endometrioid, but not mucinous.<sup>24</sup> If chronic inflammation due to ascending foreign bodies is indeed the mechanism by which talc use is associated with increased ovarian cancer risk, then these results fit the picture. The results for non-perineal application of talc were still positive but of lower magnitude, supporting the hypothesis of ascending foreign bodies causing chronic inflammation. It is plausible that non-perineal application of talc may cause increased risk through, e.g., the respiratory tract. Unfortunately, the evidence remains insufficient to understand the mechanism with any reasonable certainty.

We also found a slightly greater increased risk of ovarian cancer with >3600 lifetime applications compared with those with <3600 lifetime applications. The number of lifetime applications is a more valid measure of the patient's exposure to perineal talc than either duration or frequency of use alone. This finding also supports the chronic inflammatory hypothesis, as repeated exposure would induce a longer period of chronic inflammation, and therefore should increase the predisposition to the development of ovarian cancer. It is notable that these data were only available from

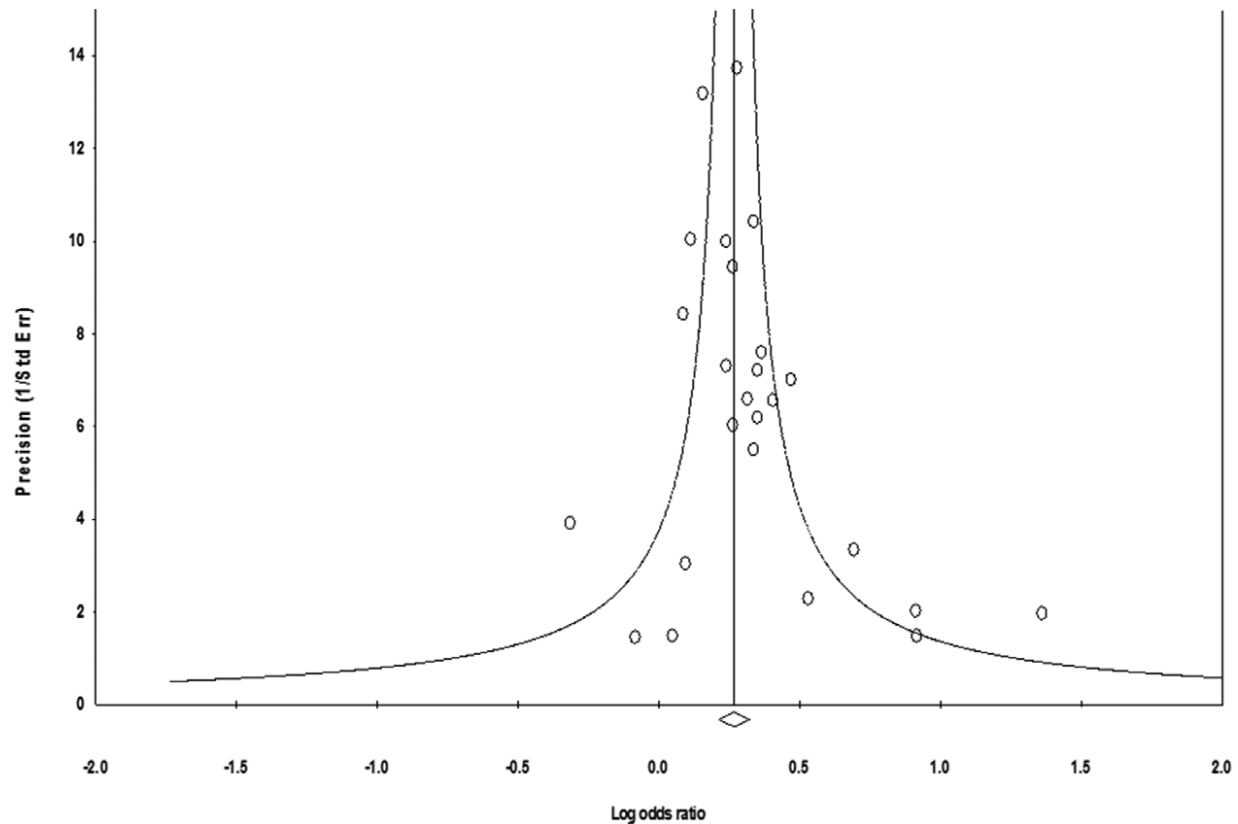


**FIGURE 2.** A, Any perineal talc use is associated with an increased risk of any ovarian cancer (OR = 1.31; 95% CI = 1.24, 1.39). B, Long-term perineal talc use (>10 years use) is associated with an increased risk of any ovarian cancer, but of a lower magnitude than any perineal use (OR = 1.25; 95% CI = 1.10, 1.43). C, Any perineal talc use is associated with an increased risk of serous ovarian cancers (OR = 1.32; 95% CI = 1.22, 1.43). D, Any perineal talc use is associated with an increased risk of endometrioid type ovarian cancers (OR = 1.35; 95% CI = 1.14, 1.60).

case-control studies, as the three cohort studies did not sufficiently record duration and frequency of use to be included in the analysis. This retrospective finding is therefore prone to recall bias.

This meta-analysis had several strengths. None of the analyses in this review had statistically significant heterogeneity, except for non-perineal application, which indicates consistency in the direction and magnitude of the effect size between individual studies, and strengthening the reliability of the pooled effect sizes. Another strength of this review is

the large number of overall cases ( $n = 14,311$ ), improving the power of the meta-analysis to detect a relatively small effect size, as occurred in this case. Another strength of this review is that the included studies were of relatively high quality as assessed through the NOS, reducing the potential for bias in the conclusions drawn. The NOS revealed that the most common limitations of the included case-control studies were the failure to blind interviewers to case-control status of subjects in the interview, and reliance on memory and self-report for collection of data on perineal talc use.



**FIGURE 3.** Funnel plot for the meta-analysis of studies examining any perineal talc use and risk of ovarian cancer ( $P = 0.09$ ).

A limitation of this study is that it pools nonrandomized studies, primarily case-control studies. The retrospective nature of case-control studies introduces the potential for recall bias. In this case, it is entirely possible that patients with ovarian cancer may be more aware of their previous talc use and hence be more likely to report higher past use. It is possible to attempt to overcome this by blinding the participants to the nature of the study, usually by asking spurious questions; however, the effectiveness of this approach may be limited.<sup>28</sup> Many of the studies in this review recorded data about talc use as part of a more extensive questionnaire focused on other associations, which may reduce the potential for recall bias. However, since the initiation of lawsuits in 2014, there has been extensive media coverage regarding this association, and the potential for recall bias in case-control studies conducted since then may be exacerbated.

Cohort studies are useful in that they are prospective; however, the low incidence of ovarian cancer results in relatively small number of cases even in large cohorts, as seen in the three cohort studies included in this review.<sup>29</sup> Considering potential exposure misclassification issues in case-control studies, the effect for any perineal talc use was very weak in a small number of cohort studies. However, an association between talc use and serous invasive ovarian cancer was found.

Of the studies in this review, case-control studies achieved much large number of cases, in some instances in excess of 2000 cases and a similar number of age-matched

controls, which provide greater statistical power for the detection of an effect size of small magnitude. Hence while case-control studies are low-level evidence, they have been preferred in the investigation of the association between talc use and ovarian cancer. They also have the important advantage of not requiring 15 or more years of follow-up, as is necessary for a cohort study to sufficient detect cases of ovarian cancer relative to certain exposures. One potential way to overcome this limitation in future studies is to ensure that talc use is always included in questionnaires of any cohort studies investigating ovarian cancer. It is important not only that talc use be investigated but also the precise location, duration, and frequency of use. As it stands, a meta-analysis of observational studies such as the present study provides the highest level of evidence practically feasible for this research question.

## CONCLUSIONS

The results of this review indicate that perineal talc use is associated with a 24%–39% increased risk of ovarian cancer. While the results of case-control studies are prone to recall bias, especially with intense media attention following the commencement of litigation in 2014, the confirmation of an association in cohort studies between perineal talc use and serous invasive ovarian cancer is suggestive of a causal association. Additional epidemiologic evidence from prospective



studies with attention to effects within ovarian cancer subtype is warranted. There is a substantial need for further research on a potential mechanism by which ovarian cancer may be caused by talc, as this will allow a causal relationship to be established or rejected with more certainty. However, particularly because of the dearth of screening tests available for this high-mortality cancer, it is important that research into this association continue as it is a potential avenue for cancer prevention.

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# Exhibit 63

# Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer

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20 **Abstract**

21 Over the past four decades, there has been increasing concern that perineal use of talc  
22 powder, a commonly used personal care product, might be associated with an  
23 increased risk of ovarian cancer.

24 **Objectives:** To systematically review all available human epidemiological data on the  
25 relationship between perineal use of talc powder and ovarian cancer, with consideration  
26 of other relevant experimental evidence.

27 **Methodology:** We identified 30 human studies for qualitative assessment of evidence,  
28 including 27 that were retained for further quantitative analysis.

29 **Results:** A positive association between perineal use of talc powder and ovarian cancer  
30 was found [OR: 1.28 (95% CI: 1.20 - 1.37)]. A significant risk was noted in Hispanics  
31 and Whites, in women applying talc to underwear, in pre-menopausal women and in  
32 post-menopausal women receiving hormonal therapy. A negative association was noted  
33 with tubal ligation.

34 **Conclusion:** Perineal use of talc powder is a possible cause of human ovarian cancer.

35 **Keywords:** Talc; ovarian cancer; perineal; epidemiological studies; systematic review;  
36 meta-analysis; toxicological studies.

## 1. Introduction

Ovarian cancer is a common gynecologic cancer among women in developed countries, occurring at low rates among young women but increasing with age [1]. The annual incidence rate of ovarian cancer during the period 2005 – 2009 was 12.7/100,000 women, varying by ethnicity. The majority of ovarian cancers are diagnosed at an advanced stage, with 61% having distant metastases at diagnosis. Hereditary risk factors for ovarian cancer, specifically BRCA1 gene mutations, increase the risk above 35 years of age by about 2-3%.

In recent decades, there has been increasing concern that perineal exposure to talc, a commonly used personal care product, might be associated with an increased risk of ovarian cancer. However, the data describing this association is somewhat inconsistent. Perineal application of talc among women varies by geographic location (Supplementary Material I), with prevalence of use generally higher in Canada, the US and the UK compared to Greece, China and Israel [2].

In order to better characterize the potential ovarian cancer risk associated with perineal use of talc, we conducted a systematic review and meta-analysis of peer-reviewed human studies on this issue. We also examined additional in-vitro or in-vivo toxicological studies, which shed light on possible biological mechanisms that might support an association between and ovarian cancer.



## **2. Materials and Methods**

### **2.1. Literature Search and Identification of Relevant Human Studies**

A comprehensive, multi-step search strategy was used to identify relevant studies on talc from multiple bibliographic databases, relevant national and international agencies and other grey literature sources (Supplementary Material II). Specifically, conducted a systematic search for all original studies involving human subjects that examined the association of genital/perineal use of talc powder and risk of ovarian cancer, including studies identified in a previous review by Berge et al. [3]. This review followed the PRISMA guidelines, and more specific guidance provided by the Cochrane Collaboration [4] (see Supplementary Material II for details).

Included studies were individually evaluated and scored by two reviewers (MT and NF), as detailed in the Table 1 and Supplementary Material XI. Studies included in previous reviews by both Berge et al. [3] and Penninkilampi et al [5] are compared in Supplementary Material I.

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [6], as detailed in Supplementary Material IV. We used a cut-off point of 7+ stars to represent studies of higher quality.

### **2.2. Literature Search and Identification of Relevant Non-Human Studies**

We conducted a (non-systematic) review of relevant non-human studies identified in three major bibliographic databases to identify potentially relevant animal

and in vitro studies (Supplementary Material V). Only studies that focused on perineal exposure to talc powder were included. For outcomes, studies that focused on any type of cancer including ovarian cancer and perineal exposure were considered. All retrieved studies were examined for relevance, reliability and overall quality using the Klimisch scoring system [7, 8] (Supplementary Material VII, VIII and IX).

Studies are classified into one of the following four categories of reliability: 1) reliable without restriction, 2) reliable with restrictions, 3) not reliable and 4) not assignable. Additionally, category (5) is assigned to special studies focusing on pharmacologic or mechanistic investigations.

### **2.3. Hazard Characterization**

Epidemiological studies included in the systematic review were qualitatively assessed to examine their potential to inform a weight of evidence analysis. Findings from these studies were evaluated with respect to study design, exposure and outcome ascertainment, as well as potential sources of bias and confounding.

Animal studies were evaluated for evidence on the association between perineal application of talc and ovarian cancer. Additional information on mechanism of action and toxicokinetics derived from in-vitro and in-vivo studies was used in evaluating biological plausibility.

We evaluated the overall weight of scientific evidence by performing a qualitative evaluation of the findings collected from epidemiological studies as well as non-human studies, using the Hill criteria [9].

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100 **2.4. Quantitative Meta-Analysis**

101 We conducted a meta-analysis of the risk of ovarian cancer in relation to perineal  
102 use of talc using quantitative risk estimates reported in 27 original studies, comprising  
103 three cohort studies and twenty-four case-control studies (included in Table 1). Studies  
104 that had analyzed overlapping study populations were assessed on a case-by-case  
105 basis for inclusion into the meta-analysis. The level of detail in the reported findings,  
106 including sample size and publication date, were considered when deciding which study  
107 to include in the case of overlap (Supplementary Material XIV).

108 Maximally adjusted odds ratios (ORs), hazard ratios (HRs) or relative risks (RRs)  
109 – measures that are largely comparable because of the relatively low rate of occurrence  
110 of ovariaion cancer – were extracted from the original studies. Details of the meta-  
111 analytic methods are provided in Supplementary Material XIV.

112

113

114 **Table 1: Characteristics and overall findings of all included studies (N=30).**

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
<b><i>Case-control studies</i></b>						
<b>Booth et al.* (1989), UK [10]</b>	235/451	Range: 20-65  Mean: 52.4 (cases); 51.4 (controls)	Frequency	No trend found	Possible association  with >weekly use.	5
<b>Chang and Risch (1997), Canada [11]</b>	450/564	Range: 35-79  Mean: 57.2 (cases); 57.5 (controls)	Ever use  Frequency  Duration  Time of use  Type of use	Possible exposure-  response with  frequency and  duration of use	Positive association	7

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<sup>1</sup> Newcastle-Ottawa Scale (NOS) score for each of the listed studies as assessed in our review

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
			Pelvic surgery			
			Histology			
<b>Chen et al.* (1992), China [12]</b>	112/224	Mean: 48.5 (cases); 49.0 (controls)	Ever use;	No trend analysis conducted	Positive association with use >3 months	6
<b>Cook et al. (1997), USA [13]</b>	313/422	Range: 20-79	Ever use  Duration  Type of use  Histology  Lifetime applications	No trend found	Positive association.	7
<b>Cramer et al. (1982), USA [14]</b>	215/215	Range: 18-80  Mean $\pm$ SD: 53.2 $\pm$ 1.0 (cases); 53.5 $\pm$ 1.0 (controls)	Ever use  Type of use  Pelvic surgery	No trend analysis conducted	Positive association	6



Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
<b>Cramer et al.</b> <b>(2016), USA [15]</b>	2,041/2,100	Range: 18-80	Ever use;  Frequency;  Duration;  Type of use;  Histology;  Type of powder;  Pelvic surgery;  Ethnicity;  Age at first use;  Time since last exposure;	Significant trend for  years since  exposure, frequency  and duration of use,  and number of  lifetime applications	Positive association	7
<b>Gates et al.</b> <b>(2008), USA [16]</b>	New England  Case Control  (NECC):  1,175/1,202  Nurses' Health	Mean ± SD: 51 ±13  (NECC);  Mean ± SD: 51 ±8  (NHS)	Ever use;  Frequency;	Significant trend for  frequency of use	Positive association	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
Study (NHS): 210/600						
<b>Godard et al.</b> <b>(1998), Canada</b> <b>[17]</b>	153/152	Mean: 53.7	Ever use;  Sporadic/familial	No trend analysis  conducted	No association	5
<b>Green et al.</b> <b>(1997), Australia</b> <b>[18]</b>	824/860	Range: 18-79	Ever use;  Pelvic surgery;	No trend found	Positive association	7
<b>Harlow et al.</b> <b>(1989), USA [19]</b>	116/158	Range: 20-79	Ever use;  Type of use;  Type of powder;	No trend analysis  conducted	No association	7
<b>Harlow et al.</b> <b>(1992), USA [20]</b>	235/239	Range: 18-76	Ever use;  Frequency;  Duration;  Type of use;	Significant trend for  monthly frequency of  use	Positive associations in certain subgroups (talc used before 1960, women <50	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
			Method of use; Histology; Tumor grade; Type of powder; Lifetime applications; Age of first use; Pelvic surgery;		years old, women with 1 or 2 live births)	
Hartge et al. (1983), USA [21]	135/171	Mean: 52.1 (cases); 52.2 (controls)	Ever use;	No trend analysis conducted	No association	5
Kurta et al. (2012), USA [22]	902/1,802	Range: No range reported (age 25+)	Ever use;	No trend analysis conducted	Positive association	6
Langseth & Kjaerheim (2004), Norway [23]	46/179	Not reported	Ever use,	No trend analysis conducted	No association	4

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
<b>Merritt et al.</b> <b>(2008), Australia</b> <b>[24]</b>	1,576/1,509	Range: 18-79  Mean: 57.8 (cases);  56.4 (controls)	Ever use;  Duration;  Histology;  Pelvic surgery;  Age at diagnosis;	No trend found	Positive association  strongest for serous  and endometrioid  subtypes.	7
<b>Mills et al.</b> <b>(2004), USA [25]</b>	249/1,105	Mean $\pm$ SD: 56.6  (cases); 55 (controls)	Ever use;  Frequency;  Duration;  Year of first use;  Histology;  Pelvic surgery;  Time of use;  Tumor behavior;  Cumulative use;	No trend found	Positive association  for invasive and  serous invasive  tumors.	6

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
<b>Moorman et al. (2009), USA [26]</b>	African- American: 143/189; White 943/868	Range: 20-74	Ever use;  Ethnicity;	No trend analysis conducted	No association	6
<b>Ness et al. (2000), USA [27]</b>	767/1,367	Range: 20-69	Ever use;  Duration;  Method of use;	No trend found	Positive association for any method of use.	6
<b>Rosenblatt et al. (1992), USA [28]</b>	77/46 (analyzed)	Range: ≤30 – 80≥	Ever use;  Duration;  Type of use;  Pelvic surgery;	Positive trend for duration of use since tubal ligation	Possible association	4
<b>Rosenblatt et al. (2011), USA [29]</b>	812/1,313	Range: 35-74	Ever use;  Lifetime number of applications;  Duration;	No trend found	Possible association	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
			Year of first use; Age of first use; Age of last use; Time of use; Type of use; Histology;			
Schildkraut et al. (2016), USA [30]	584/745	Range: 20-79	Ever use; Frequency; Duration; Histology; Lifetime applications; Menopausal status;	Significant trend with frequency and duration of use, and number of lifetime applications	Positive association	8
Tzonou et al. (1993), Greece [31]	189/200	Range: <70	Ever use;	No trend analysis conducted	No association	5



Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
<b>Whittemore et al.</b> <b>(1988), USA [32]</b>	188/539	Range: 18-74	Ever use;  Frequency;  Duration;  Type of use;  Pelvic surgery;	No trend found	Could neither  implicate nor  exonerate talc as an  ovarian carcinogen	4
<b>Wong et al.</b> <b>(1999, 2009),</b> <b>USA [33, 34]</b>	462/693	Mean: 54.9	Ever use;  Type of use;  Duration;  Pelvic surgery;	No trend found	No association	4
<b>Wu et al. (2015),</b> <b>USA [35]</b>	1,701/2,391	Range: 18-79	Ever use;  Ethnicity;	No trend analysis  conducted	Positive association  among Hispanics  and non-Hispanic  whites, but not  African Americans.	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
Wu et al. (2009), USA [34]	609/688	Range: 18-74	Ever use;  Frequency;  Duration;  Type of use;  Histology;  Time of use;  Cancer stage;	Significant trend for  frequency and  duration of use, and  number of lifetime  applications	Positive association	7
<b>Cohort studies</b>						
Gates et al. (2010)*, USA [36]	797/108,870	Range: 30-55	≥/week vs <1/week;  Histology;	No trend analysis  conducted	Possible association  that varies by  histological subtype.  No association with  mucinous tumors.	7

Study (Location)	Sample Size (Cases/ Controls or Cases/ Total Cohort)	Age (Years)	Subgroup Analyses	Exposure-Response Assessment	Overall Author Conclusion	NOS <sup>1</sup>
<b>Gertig et al.</b> <b>(2000), USA [37]</b>	307/78,630	Range: 30-55 (at cohort entry)	Ever use; Frequency; Histology; Race;	No trend found	Possible association (modest increase for serous invasive subtype)	5
<b>Gonzalez et al.</b> <b>(2016), USA [38]</b>	154/41,654	Range: 35-74 Median: 57.8	Ever use; Time of use;	No trend analysis conducted	No association	6
<b>Houghton et al.</b> <b>(2014), USA [39]</b>	429/61,285	Range: 50-79 Mean: 63.3	Ever use; Duration; Type of use; Histology;	No trend found	No association	7

\* Study assessed for qualitative evidence but not included in the meta-analysis

### 3. Results

#### 3.1. Evidence from Human Studies

The multiple database search for original human studies yielded 656 references. Although grey literature search yielded another 477 references, only 5 were judged relevant to the present analysis. Automatic followed by manual removal of duplicates identified 282 references for screening and review.

Multi-level screening and full-text examination resulted in the inclusion of 30 studies for further qualitative/quantitative analyses (Supplementary Materials X and XI). A detailed PRISMA flow diagram is shown in Figure 1 [40]. Key characteristics of the included 26 case-control studies and four cohort studies are summarized in Table 1.

Twenty-one of the thirty studies were carried out in the USA, with the remaining studies conducted in Europe (n=4), Canada (n=2), Australia (n=2) and China (n=1). Forty percent (n=12) of the studies were relatively recent, published in the last decade, with the remaining studies published between 1982 and 2006. The study populations generally included adult women. Several studies analyzed data from populations initially recruited for other purposes, such as the Nurses' Health Study (NHS) [15, 36, 37] and Women's Health Initiative (WHI) [39].

The number of ovarian cancer patients analyzed varied from as few as 46 cases [23] to 22,041 cases [15]. Twenty-seven out of the 30 included studies assessed the association between ever use of perineal talc use and ovarian cancer. Subgroup

analyses examining the effect of frequency and duration of use, type of use, period of  
use and other factors varied among these studies (Table 1).

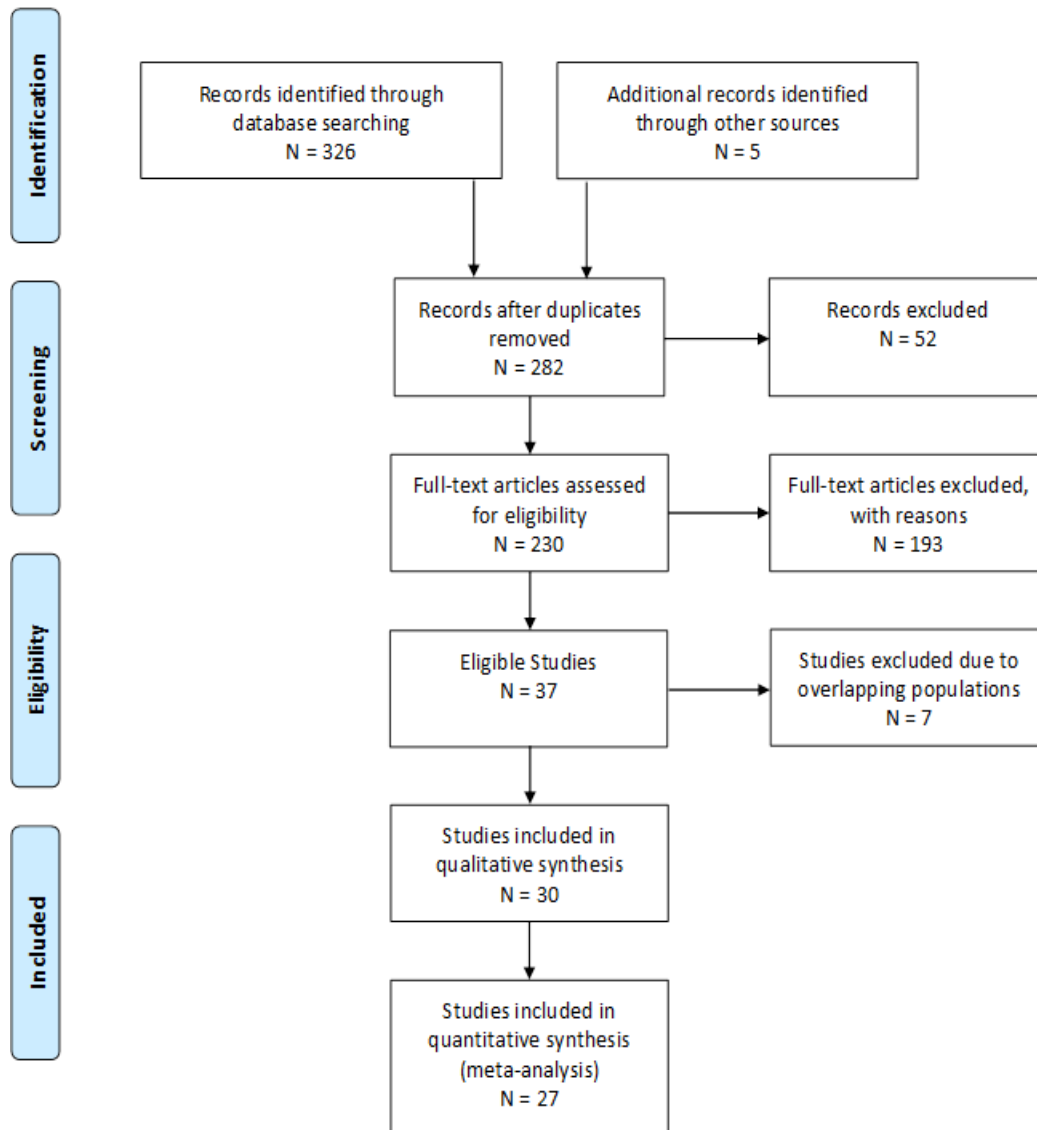


Figure 1: PRISMA Flow Diagram

Sixty three percent (n=19) of the studies concluded the presence of a positive  
association between perineal exposure to talc powder and ovarian cancer risk [10-16,

18, 20, 22, 24, 25, 27-30, 34-36]. Ten studies concluded the absence of an association [17, 19, 21, 23, 26, 31, 33, 37-39]. Only one study could not reach a clear conclusion on the presence or absence of an association [32]. Many of the included studies reported variability in some of the analyzed subgroups regarding possible association between exposure to talc powder and risk of ovarian cancer. Supplementary Material X presents the findings and details of all the studies included in the analysis, while Supplementary Material XI summarizes the strengths and limitations of each of these studies as identified by the original study authors and by us.

## **3.2. Evidence from Non-Human studies**

After removal of duplicates, the bibliographic database searches on non-human studies initially yielded 1,165 references. The 51 retained animal studies focusing on the carcinogenicity of talc, mechanism of action, and toxicokinetics are summarized in Supplementary Material XII.

## **3.3. Hazard Characterization**

### **3.3.1. Evidence from Human Studies**

The case-control studies generally included adult women participants. Cases were commonly selected from registries or hospital records, and included all eligible subjects within a specific geographic region and diagnosed with ovarian cancer within a predetermined time period. Controls were generally matched to cases by age and residence. All the included studies compared the risk of ovarian cancer in ever vs never

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users of talc (perineal application). However, several of the studies also included subgroup analyses to examine the potential effect of frequency of use, duration of use, tumor histology, ethnicity, method of use, lifetime number of applications, year of first use, and menopausal status. Some authors concluded that the risk of ovarian cancer is limited to [or stronger in] certain subgroups (weekly talc users, premenopausal women) or for specific histology types (notably serous tumors).

Studies reported effect estimates adjusted for a variety of potential confounders (see detailed tables in Supplementary Material X & XI). Age and parity were considered the two most important variables that could introduce potential bias, based on prior literature: few studies reported findings that were not adjusted for these two variables. As many of the studies only reported on the ovarian cancer risk assessing only one exposure category (comparing only ever vs never users of talc), exposure-response analyses were not done in all studies. When conducted, findings from trend analyses were not consistent.

### **3.3.2. Evidence from Non-Human Studies**

The following aspects were considered in the weight of evidence assessment of ovarian cancer and perineal exposure to talc:

- hazards arising from the physical and chemical properties of talc, including potential structure-activity relationship indicative of carcinogenic potential;
- the toxicokinetics of talc and the ability to migrate from the perineal area to ovaries and quantity at the actual target site (the tissue dose);

- evidence on ovarian cancer reported in animal studies; and
- findings from in vitro studies suggestive of mechanism of action of carcinogenic effect.

While the data from the animal studies considered various routes of talc administration are inconsistent [41-46], there are observations from in vivo and in vitro studies which support the potential for local carcinogenic action of talc on fallopian, ovarian and peritoneal epithelium [27, 47-53].

The results from the *in vitro* studies are informative for mechanisms of action of possible carcinogenicity. Smith and colleagues [54] identified 10 key characteristics (KCs) commonly exhibited by established human carcinogens.

Oxidative stress (KC 6) and inflammation (KC 5) in cell cultures induced by talc have been reported by several authors [48], corresponding to two of the 10 key characteristics (KCs) described by Smith et al. [54]. Several authors suggested additional potential mechanisms of action through cell proliferation (KC 10) and changes in gene expression, presumably facilitated by oxidative stress and dysregulated antioxidant defense mechanisms [49, 55].

Chronic perineal or vaginal exposures of animals to talc do not directly affect ovulation or steroidal hormone levels, but can induce chronic local inflammation, which has been suggested as a risk factor for ovarian cancer [56]. Mechanism of action studies suggested that talc can complex iron on the surface and disrupt iron homeostasis, associated with oxidant generation, macrophage distress and leukotriene

released by macrophages in the surrounding cells resulting in the inflammatory response which could act as a tumor promoter in both animals and humans [48, 50, 51].

The changes seen in cultured cells after exposure to talc [50, 51] are consistent with those inflammatory and proliferative processes in the lungs seen in laboratory animals after inhalation exposure in a 1993 study conducted by the US National Toxicology Program [47]. In female rats, hyperplasia of alveolar epithelium was associated with inflammatory response and occurred in or near foci of inflammation [47]. The severity of the fibrous granulomatous inflammation in the lungs increased with increased talc concentrations and exposure duration and a significant association was observed between inflammation and fibrosis in the lungs and the incidence of pheochromocytomas in this study [47]. Overall, the available experimental data suggest irritation, followed by oxidative stress and inflammation, may play be involved in local carcinogenic effects of talc in the ovaries.

Local inflammation of the epithelial ovarian surface in rats following by injection of a suspension of talc particles demonstrated the development of foreign body granulomas surrounding talc particles and large ovarian bursal cysts [53]. It is generally accepted that benign and malignant ovarian epithelial tumors arise from surface epithelium and its cystic derivatives, and surface epithelial cysts have a greater propensity to undergo neoplasia than does the surface epithelium itself [57]. Evidence of neoplasms of epithelial origin, nuclear atypia, or mitotic activity in the surface epithelium was not found in this study; however, focal areas of papillary changes in the surface epithelium consistent with the histological signs of premalignancy were observed in 40% of treated animals [53].

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Data on talc migration in the genital tract of animals is inconsistent, but could not exclude such possibility [58-61]. Some studies have reported lack of neutron-activated talc migration from the vagina to the ovaries in cynomolgus monkeys [58], but talc particles were identified in the ovaries of rats that received intrauterine instillation of talc [60]. Radioactivity was not found in the ovaries of rabbits dosed intravaginally with tritium-labelled talc, but was detected in cervix and fallopian tubes [59-61]. In studies in humans, Henderson and colleagues [62] examined tumor tissue of female patients with ovarian and cervical tumors. The authors detected talc particles in histological samples from 10 of 13 ovarian tumors, 12 of 21 cervical tumors and in 5 samples of 12 normal ovarian tissues [62].

Historically, the concern for talc carcinogenicity has been associated with its contamination by asbestos fibers (tremolite) [63], which is considered carcinogenic to humans [2]. Talc, including baby powder, available in the US, contains only U.S. Pharmacopeia (USP) grade pure talc [64]. Talcum powder has been asbestos-free since the 1976 where the specifications for cosmetic talc were developed [65].

### **3.3.3. Weight of evidence for carcinogenicity**

Based on our evaluation of the weight of multiple lines of evidence, we concluded that perineal application of talc is a possible cause of ovarian cancer in humans. In 2010 the International Agency for Research on Cancer [2] categorized perineal use of talc-based body powder (not containing asbestos or asbestiform fibers) as “possibly carcinogenic to humans (Group 2B)” [66].

Table 2 summarizes the available evidence for the association of ovarian cancer with perineal application of talc, organized around the nine Hill criteria [9]. Additional details of this evaluation are given in Supplementary Material XIII.

**Table 2: Summary of evidence for each of the Hill Criteria of causation, as applied to perineal application of talc and ovarian cancer**

Criterion	Summary of Evidence
<b>Strength of association</b>	<ul style="list-style-type: none"> <li>Out of the 30 epidemiological studies, six reported positive association of statistical significance with a risk value (relative risk or odds ratio) of 1.5 or greater</li> <li>None of the cohort studies (n=3) found statistically significant association</li> </ul>
<b>Consistency</b>	<p>Fifteen out of thirty studies reported positive and significant associations reported in:</p> <ul style="list-style-type: none"> <li>Different ethnicities (Caucasians, African Americans, and Latin Americans);</li> <li>Over four decades (1982 - 2016);</li> <li>Mostly in studies from the United States but also in other countries (Canada, Australia and China)</li> <li>Case-control studies but not in cohort studies</li> </ul>
<b>Specificity</b>	<ul style="list-style-type: none"> <li>Overall, the perineal talc exposure is specifically associated with cancer of the ovary and not other organs</li> <li>No evidence of other target organs (e.g., liver) being associated with perineal application of talc (via systemic exposure)</li> </ul>

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Criterion	Summary of Evidence
	<ul style="list-style-type: none"> <li>Thirteen studies included analyses by histologic type of ovarian cancer, and eight of them found a significant increase in the risk of serous ovarian cancer in talc users</li> </ul>
<b>Temporality</b>	<ul style="list-style-type: none"> <li>In all case-control studies reporting positive outcome, the participants recalled that exposure to talc preceded the reported outcome</li> <li>In cohort studies, the follow up period could have been inadequate (&lt;15 years) to detect a potential association between talc exposure and ovarian cancer</li> </ul>
<b>Biological gradient (exposure-response)</b>	<ul style="list-style-type: none"> <li>About half of the epidemiological studies assessed only one level of talc exposure (ever vs never usage)</li> <li>Of the 12 studies reporting a positive association, six studies found significant exposure-response trend, particularly with medium and high frequency usage groups Regarding duration of use/exposure to talc, several studies reported the greatest risk in the 20+ years of use exposure group, followed by the 10-20 years' group, then the &lt;10 years' group</li> </ul>
<b>Biological plausibility</b>	<ul style="list-style-type: none"> <li>Particles of talc appear to migrate into the pelvis and ovarian tissue causing irritation and inflammation</li> <li>Transport of talc via perineal stroma and presence in ovaries documented</li> <li>Chronic inflammatory response and alteration in local immunogenicity are possible mechanisms</li> </ul>
<b>Coherence</b>	<ul style="list-style-type: none"> <li>Results from talc epidemiology studies are coherent with the current knowledge on the risk factors for ovarian cancer (e.g., factors/physiological states associated with greater frequency and duration of ovulation are associated with increased risk of ovarian cancer)</li> </ul>

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Criterion	Summary of Evidence
	<ul style="list-style-type: none"> <li>Many (but not all) case-control studies reported lower risk of ovarian cancer in women who underwent pelvic surgery or tubal ligation (which disrupts the pathway and movement of talc from lower to upper genital tract) &amp; suppressed ovulation</li> </ul>
<b>Experimental evidence</b>	<ul style="list-style-type: none"> <li>Perineal application of talc has not been tested in an animal model of ovarian cancer</li> <li>The single animal cancer bioassay with talc conducted by the US National Toxicology Program was only by the inhalation route</li> <li>Rodent models may be of limited relevance because of ovulations occurring only or mainly during the breeding season and the rarity of ovarian epithelial tumors in these animals and ovaries are variously enclosed in an ovarian bursa.</li> </ul>
<b>Analogy</b>	<ul style="list-style-type: none"> <li>Talc and asbestos are both silicate minerals</li> <li>Talc has been variably contaminated with asbestos (tremolite and anthophyllite; until 1976, talcum powders were only required to contain at least 90% mineral talc)</li> <li>The pleural and peritoneal mesotheliomas caused by asbestos are histologically similar to epithelial ovarian cancer associated with talc</li> <li>In animal models, asbestos induces ovarian epithelial hyperplasia similar to early epithelial tumors reported in women with past use of talc</li> </ul>

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261 **3.4. Meta-Analysis**

262 The use of genital talc was associated with a significant increase in the risk of  
263 epithelial ovarian cancer, with an overall odds ratio [OR] based on our meta-analysis of  
264 1.28 (95% confidence interval [CI]: 1.20 to 1.37  $P < 0.0001$ ,  $I^2 = 33\%$ ), as presented in

Figure 2. This result is comparable to those of earlier meta-analyses conducted by other investigators [3, 5, 67-69] as shown in Supplementary Material I.

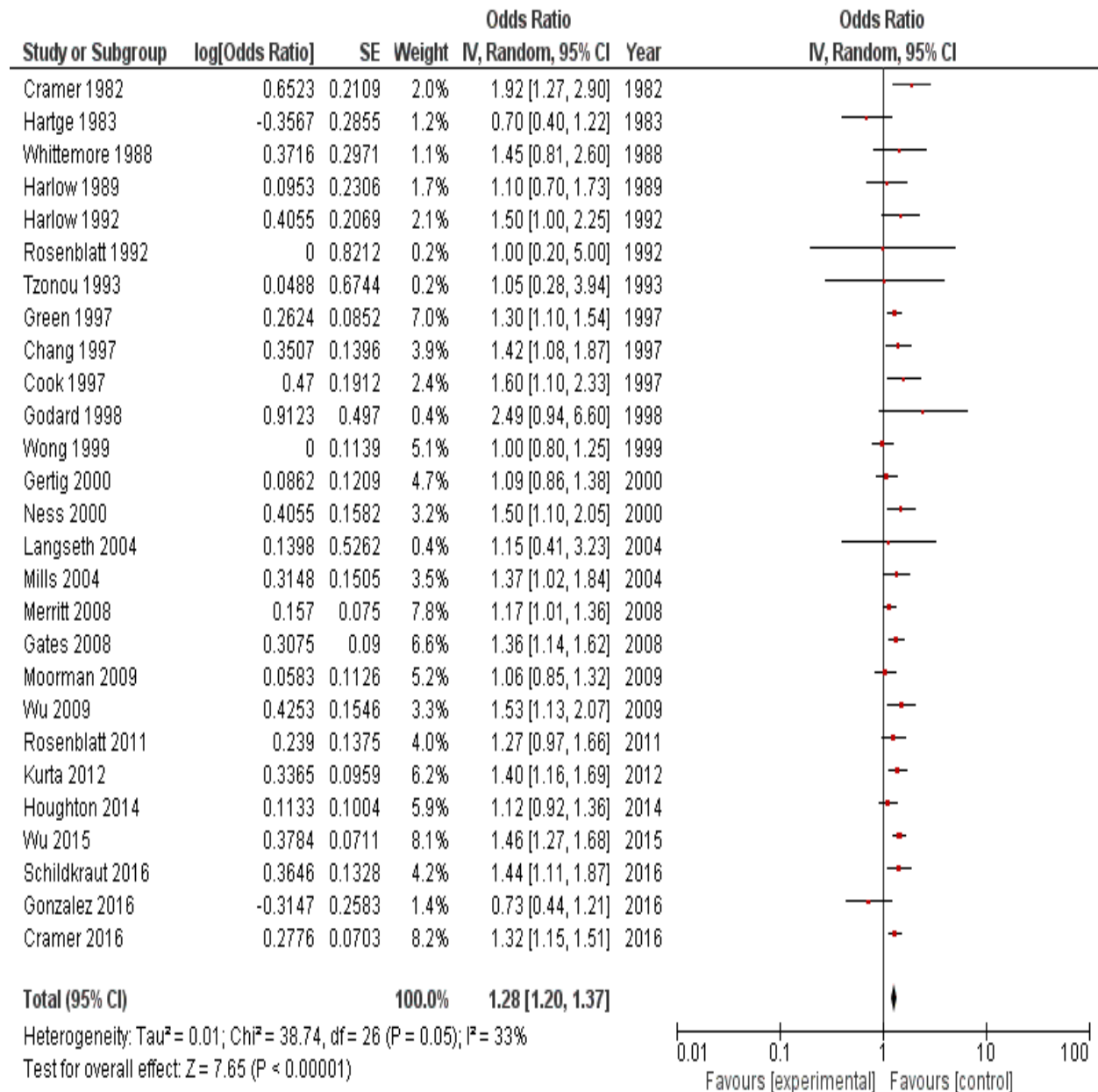


FIGURE 2: Forest plot of the meta-analysis results on perineal use of talc and risk of ovarian cancer

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271           An increased risk is more apparent in Hispanics and Whites, in women applying  
272 talc to underwear, in pre-menopausal women and post-menopausal women receiving  
273 hormonal therapy, as well as for the serous and endometrioid types of ovarian cancer  
274 (Table 3 and Supplementary Material XIV). A negative association was noted with tubal  
275 ligation. Our analysis pooled risk estimates from 27 original studies including 3 cohort  
276 studies and 24 case-control studies, spanning across four decades (1982-2016) and  
277 including a total of 16,352 cases and 19,808 controls from different ethnicities.

278           In assessing heterogeneity among included studies, most subgroup analyses  
279 reported an  $I^2$  statistic ranging between 0%-40%, which will have only a minimal impact  
280 on the analysis [4]. Only three subgroup analyses (ethnicity, menopausal state, and  
281 pelvic surgery) reported an  $I^2$  statistic of 77%-78%, where considerable heterogeneity  
282 might have had an impact on the results [4]. (See Table 3 and Supplementary Material  
283 XIV for a listing of  $I^2$  statistic values for the different subgroup analyses)

284           Whereas case-control studies showed a significant increase in the risk of ovarian  
285 cancer for ever vs never users of talc powder [OR: 1.32 (95% CI: 1.24 to 1.40),  $P <$   
286 0.00001,  $I^2 = 22\%$ ], cohort studies failed to show a significant increase in risk [OR: 1.06  
287 (95% CI: 0.9 to 1.25),  $P = 0.49$ ,  $I^2 = 17\%$ ]. Thirteen out of 24 case-control studies (54%)  
288 showed a statistically significant association, whereas none of the 3 cohort studies  
289 showed a significant overall association between ever vs never genital talc exposure  
290 and risk of ovarian cancer.

Subgroup analysis by study quality (NOS $\geq$ 7 vs NOS<7) did not show any significant differences in the overall pooled risk estimate. Similarly, there were no differences among subgroup analysis conducted by decade of publication. A significant association was observed for population-based studies [OR: 1.34 (95% CI: 1.27 to 1.41),  $P < 0.00001$ ,  $I^2 = 0\%$ ], but for enlisting hospital-based controls [OR: 0.96 (95% CI: 0.78 to 1.17),  $P = 0.66$ ,  $I^2 = 0\%$ ].

We conducted influence analysis to examine the impact of individual studies on the results of our meta-analysis. No appreciable changes were observed regarding the overall association of perineal talc exposure and the risk of ovarian cancer in response to the exclusion of any one study. Detailed results from the influence analysis are provided (Supplementary Material XIV).

Subgroup analysis based on ethnicity indicated that Hispanic women using talc showed the most significant increase in risk of ovarian cancer [OR: 1.70 (95% CI: 1.17 to 2.47),  $P = 0.005$ ,  $I^2 = 0\%$ ], followed by White women [OR: 1.28 (95% CI: 1.10 to 1.49),  $P = 0.001$ ,  $I^2 = 56\%$ ]. African-American women showed a non-significant association with ovarian cancer in [OR: 1.67 (95% CI: 0.90 to 3.10),  $P = 0.1$ ,  $I^2 = 48\%$ ].

Analyzing exposure by frequency of talc use, talc exposure was stratified into three groups: high (once daily for >25 days/month), medium (once daily for 10–25 days/month) and low (once daily for 1–<10 days/month). The OR for the high-use group was higher in the high-use group compared to the other two groups (medium and low-use groups). Duration of talc use was stratified into three groups: <10 years, 10 – <20 years, and 20+ years. The overall odds ratio of the <10 years' group was lower than the

OR for the 10 – <20 years' group. On the other hand, the OR for the 20+ years' group was lower and not statistically significant. However, this OR was based on two studies that showed considerable heterogeneity ( $I^2=75\%$ ). Examining the method of application of talc, application to the underwear subgroup had a statistically significant OR, which was the highest among all subgroups. Diaphragm use showed an expected, yet non-significant, negative association with ovarian cancer, which may be due to its action blocking the ascent of talc particles up the reproductive tract.

Pooled risk estimates were statistically significant for two histological types of ovarian cancer: serous tumors [OR: 1.38 (95% CI: 1.22 to 1.56),  $P < 0.00001$ ,  $I^2= 0\%$ ] and endometrioid tumors [OR: 1.39 (95% CI: 1.05 to 1.82),  $P= 0.03$ ,  $I^2= 2\%$ ]. The mucinous type showed a non-significant association [OR: 1.05 (95% CI: 0.85 to 1.29),  $P= 0.41$ ,  $I^2= 23\%$ ], while there were not sufficient studies to examine the other types of ovarian cancers. Regarding tumor behavior, there was no appreciable difference between invasive [OR: 1.38 (95% CI: 1.15 to 1.65),  $P= 0.0004$ ,  $I^2= 0\%$ ] and borderline [OR: 1.43 (95% CI: 1.08 to 1.89),  $P= 0.01$ ,  $I^2= 19\%$ ] grades of ovarian cancer. Borderline serous tumors showed slightly greater risk [OR: 1.39 (95% CI: 1.09 to 1.78),  $P= 0.008$ ,  $I^2= 0\%$ ] compared to the serous invasive grade [OR: 1.32 (95% CI: 1.13 to 1.54),  $P= 0.0004$ ,  $I^2= 24\%$ ], while both showed a significant association with perineal talc exposure. However, the mucinous tumors showed a non-significant association with talc exposure, with invasive grades being associated with a greater risk [OR: 1.34 (95% CI: 0.48 to 3.79),  $P= 0.58$ ,  $I^2= 70\%$ ] compared to the borderline grade [OR: 1.18 (95% CI: 0.76 to 1.82),  $P < 0.46$ ,  $I^2= 34\%$ ].



Among post-menopausal women, those receiving hormonal therapy showed the greatest risk [OR: 2.28 (95% CI: 1.72 to 3.01),  $P < 0.00001$ ,  $I^2 = 0\%$ ], followed by pre-menopausal women [OR: 1.42 (95% CI: 1.16 to 1.75),  $P = 0.0008$ ,  $I^2 = 0\%$ ], and then post-menopausal women not receiving hormonal therapy [OR: 1.05 (95% CI: 0.84 to 1.32),  $P = 0.66$ ,  $I^2 = 25\%$ ]. This subgroup analysis suggests that hormonal factors, especially estrogens influence the risk of developing ovarian cancer among postmenopausal women who have perineal talc exposure.

Women with prior ligation of the Fallopian tubes showed a significant reduction in risk [OR: 0.64 (95% CI: 0.45 to 0.92),  $P = 0.02$ ,  $I^2 = 19\%$ ] against ovarian cancer compared to hysterectomy [OR: 0.89 (95% CI: 0.54 to 1.46),  $P = 0.65$ ,  $I^2 = 61\%$ ], whereas both surgeries combined showed no effect [OR: 1.06 (95% CI: 0.78 to 1.42),  $P = 0.72$ ,  $I^2 = 61\%$ ]. This might be attributed to the fact that tubal ligation is usually performed at an earlier age, thus preventing entry of talc into the reproductive tract earlier and prolonged exposure to talc, compared to hysterectomy that is performed later in life where a higher exposure has already taken place. In a recent meta-analysis [70], the authors reported a negative association of tubal ligation (27 studies) and hysterectomy (15 studies) with the risk of ovarian cancer: this negative association was more apparent in women who had the surgery at an earlier age. A highly plausible mechanism for this association, as suggested by the authors, involves blocking of ascent of agents such as talc to the ovaries.

A summary of results of our meta-analysis is shown in Table 3. Forest plots of all sub-group analyses are provided in Supplementary Material XIV.

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359 **Table 3: Results of the subgroup analysis of talc exposure and ovarian cancer**

Outcome or Subgroup	Studies	Effect Estimate [95% CI]	Heterogeneity $I^2$ Statistic [p-value]
<b>1. Talc use</b>			
Ever vs. Never	27	1.28 [1.20, 1.37]	33% [ $< 0.00001$ ]
Ethnicity	3		77% [0.08]
<i>African Americans</i>	3	1.67 [0.90, 3.10]	48% [0.10]
<i>Hispanics</i>	2	1.70 [1.17, 2.47]	0% [0.005]
<i>Whites</i>	3	1.28 [1.11, 1.49]	56% [0.001]
<i>Asians</i>	1	0.04 [0.01, 0.16]	N/A
<b>2. Study Assessment</b>			
2.1. Study Design	27		33% [ $< 0.00001$ ]
<i>Case-Control</i>	24	1.32 [1.24, 1.40]	22% [ $< 0.00001$ ]
<i>Cohort</i>	3	1.06 [0.90, 1.25]	17% [0.49]
2.2. Type of Controls	24		22% [ $< 0.00001$ ]
<i>Hospital-based</i>	4	0.96 [0.78, 1.17]	0% [0.66]
<i>Population-based</i>	19	1.34 [1.27, 1.41]	0% [ $< 0.00001$ ]
<i>Combined</i>	1	1.45 [0.81, 2.60]	N/A
2.3. Quality Score (NOS)	27		33% [ $< 0.00001$ ]
<i>NOS <math>\geq 7</math></i>	12	1.32 [1.25, 1.40]	0% [ $< 0.00001$ ]
<i>NOS <math>&lt; 7</math></i>	15	1.21 [1.05, 1.39]	47% [0.009]
2.4. Publication Year	27		33% [ $< 0.00001$ ]
<i>1980-1989</i>	4	1.23 [0.81, 1.88]	66% [0.33]
<i>1990-1999</i>	8	1.30 [1.13, 1.50]	24% [0.0003]
<i>2000-2009</i>	8	1.25 [1.14, 1.37]	18% [ $< 0.00001$ ]
<i>2010 and beyond</i>	7	1.31 [1.18, 1.45]	44% [ $< 0.00001$ ]
<b>3. Talc Exposure</b>			
3.1. Frequency of Use	7		35% [ $< 0.00001$ ]
<i>Low</i>	5	1.22 [0.96, 1.54]	54% [0.10]
<i>Medium</i>	2	1.22 [0.98, 1.53]	0% [0.08]
<i>High</i>	7	1.39 [1.22, 1.58]	23% [ $< 0.00001$ ]
3.2. Duration of Use	6		5% [0.0008]
<i>&lt;10 Years</i>	5	1.22 [1.03, 1.45]	0% [0.02]

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Outcome or Subgroup	Studies	Effect Estimate [95% CI)	Heterogeneity $I^2$ Statistic [p-value]
10 - <20 Years	2	1.42 [1.02, 1.99]	0% [0.04]
20+ Years	2	1.19 [0.71, 1.98]	75% [0.51]
3.3. Method of Use	13		52% [0.001]
Sanitary Napkin	11	1.12 [0.91, 1.39]	50% [0.29]
Diaphragm	10	0.87 [0.72, 1.05]	25% [0.14]
Underwear	2	1.70 [1.27, 2.28]	0% [0.0004]
Male Condom	3	0.99 [0.73, 1.32]	0% [0.92]
<b>4. Tumor Histology</b>			
4.1. Tumor Histology	8		23% [< 0.00001]
Serous	7	1.38 [1.22, 1.56]	0% [< 0.00001]
Mucinous	5	1.05 [0.85, 1.29]	23% [0.41]
Endometrioid	6	1.39 [1.05, 1.82]	2% [0.03]
Clear Cell	1	0.63 [0.15, 2.65]	
<b>5. Tumor Behavior</b>			
5.1. All Grades	4		0% [< 0.00001]
All Invasive	3	1.38 [1.15, 1.65]	0% [0.0004]
All Borderline	4	1.43 [1.08, 1.89]	19% [0.01]
5.2. Serous	5		0% [< 0.00001]
Serous Invasive	5	1.32 [1.13, 1.54]	24% [0.00004]
Serous Borderline	3	1.39 [1.09, 1.78]	0% [0.008]
5.3. Mucinous	3		38% [0.40]
Mucinous Invasive	2	1.34 [0.48, 3.79]	70% [0.58]
Mucinous Borderline	3	1.18 [0.76, 1.82]	34% [0.46]
5.4. Endometrioid	1		N/A
Endometrioid Invasive	1	1.38 [1.06, 1.80]	
5.5. Clear Cell	1		N/A
Clear Cell Invasive	1	1.01 [0.65, 1.57]	
<b>6. Modifiers</b>			
6.1. Menopausal State	2		78% [0.007]
Pre-menopausal	2	1.42 [1.16, 1.75]	0% [0.0008]
Post-Menopausal (HT)	2	2.28 [1.72, 3.01]	0% [< 0.00001]
Post-Menopausal (no HT)	2	1.05 [0.84, 1.32]	25% [0.66]

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Outcome or Subgroup	Studies	Effect Estimate	Heterogeneity $I^2$
		[95% CI)	Statistic [p-value]
6.2. Pelvic Surgery	7		78% [0.35]
<i>Tubal Ligation</i>	3	0.64 [0.45, 0.92]	19% [0.02]
<i>Hysterectomy</i>	4	0.89 [0.54, 1.46]	61% [0.65]
<i>Combined</i>	4	1.06 [0.78, 1.42]	61% [0.72]

\* **NOS:** Newcastle-Ottawa Scale for quality scoring of observational studies

\*\* **Low:** Once daily for 1 – <10 days/month; **Medium:** Once daily for 10 –25 days/month; **High:** Once daily for >25 days/month

### 3.5. Exposure-Response Assessment

The effect of increasing frequency or duration of perineal use of talc and the risk of ovarian cancer was assessed in the majority of the studies included in this review. Conflicting findings were reported on the nature of the exposure-response relationship: 11 studies concluded that there is no exposure-response, five studies reported a significant positive trend with either frequency or duration of talc use, and two studies concluded that there might be an exposure-response. The remaining twelve studies did not perform or report on trend analyses.

Findings from the seven studies that indicated a potential increased risk of ovarian cancer associated with increasing use of talc are presented in Table 4. The study by Cramer et al. [15] provides the strongest evidence of an exposure-response relationship and could be considered as a key study for exposure-response assessment. The data used in this study were generated from the Nurses' Health Study

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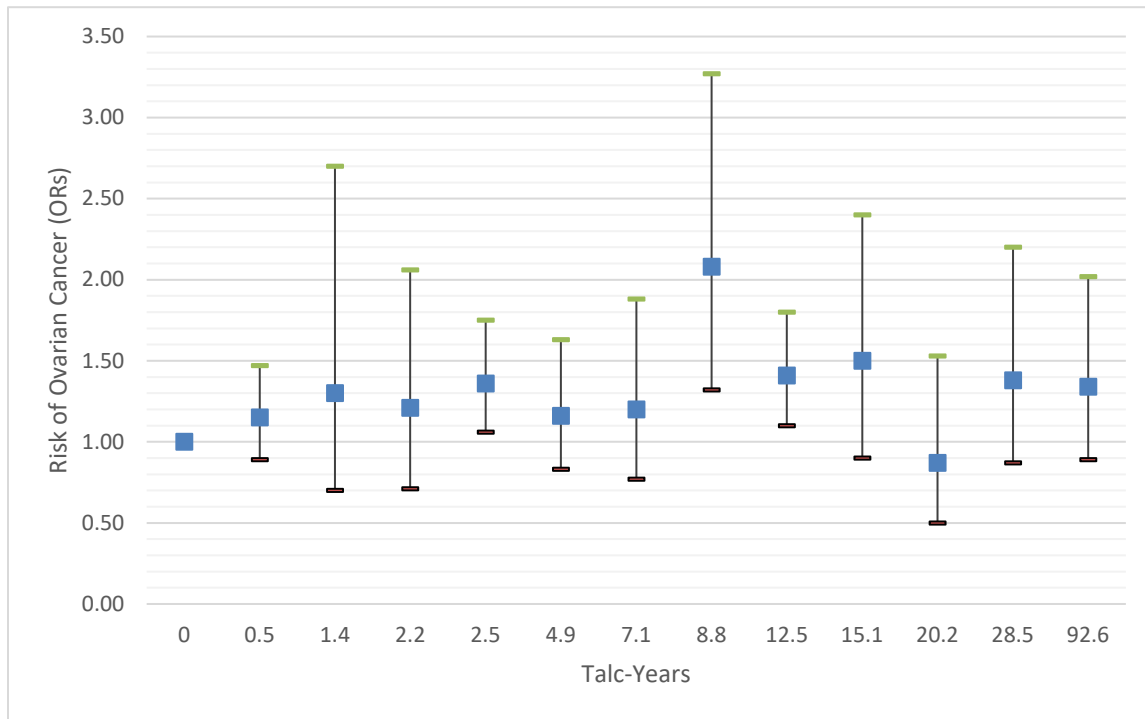
originally conducted by Belanger et al. [71], a well-designed high quality cohort study of the factors affecting women's health. The results of this study show an increased risk of ovarian cancer at the three highest exposure categories in this study, with the risk at the lowest exposure level [OR: 1.15 (95% CI: 0.89 to 1.47)] being numerically, although not significantly, elevated. Other studies in Table 4 have provided findings in support of an exposure response based on increasing number of talc applications [20, 30, 34].

In order to permit more direct comparisons of the exposure-response findings from these studies, and whenever the original study data permits, we standardized exposure measurements into talc-years as shown in Figure 3. Data points were selected from studies after excluding potential data points that are lacking precise information on the level of exposure to talc. The mid-point of the exposure categories in the exposure-response studies was used for exposure-response assessment.

Overall, the graphical results shown in this Figure 3 suggest a possible increasing trend in ovarian cancer risk with increasing cumulative exposure to talc; however, there is also a high degree of uncertainty surrounding many of the individual risk estimates. (A formal statistical test for trend was not attempted because of the high degree of heterogeneity among studies noted previously in our meta-analysis discussed in section 3.4.)



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400 **Figure 3: Ovarian cancer risk estimates at increasing levels of exposure to talc, as**  
401 **reported from multiple studies**

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405 **Table 4: Summary of studies that reported ORs for increasing number of lifetime perineal talc applications**

Study	Stratification	Reported Exposure-Response Strata	aOR*	95% CI
Schildkraut et al. (2016) [30]	Lifetime genital powder	<3,600 applications, any genital use vs (never use)	1.16	[0.83, 1.63]
		>3,600 applications, any genital use vs (never use)	1.67	[1.23, 2.26]
Whittemore et al. (1988) [32]	Overall trend	Overall trend for 30 uses per month	1.3	[0.88, 1.92]
Wu et al. (2009) [34]	By total times of talc use	≤ 5,200 times vs nonuse	1.2	[0.77, 1.88]
		5,201 – 15,600 times vs nonuse	1.38	[0.87, 2.20]
		15,601 – 52,000 times vs nonuse	1.34	[0.89, 2.02]
		> 52,000 times	1.99	[1.34, 2.96]
Mills et al. (2004) [25]	By cumulative use (frequency × duration)	First quartile (lowest exposure)	1.03	[0.59, 1.80]
		Second quartile	1.81	[1.10, 2.97]
		Third quartile	1.74	[1.11, 2.73]
		Fourth quartile (highest exposure)	1.06	[0.62, 1.83]
Rosenblatt et al. (2011) [29]	By lifetime number of applications of perineal powder after bathing	1-1,599 applications	1.21	[0.71, 2.06]
		1,600-4,799 applications	2.08	[1.32, 3.27]
		4,800-9,999 applications	0.87	[0.50, 1.53]
		≥10,000 applications	0.87	[0.48, 1.57]
Cramer et al. (2016) [15]	By total genital applications	≤360 total genital applications	1.15	[0.89, 1.47]
		361-1,800 total genital applications	1.36	[1.06, 1.75]
		1,801-7,200 total genital applications	1.41	[1.10, 1.80]
		>7,200 total genital applications	1.39	[1.11, 1.75]
Harlow et al. (1992) [20]	Total Lifetime Perineal Applications*	< 1,000 applications	1.3	[0.7, 2.7]
		1,000 - 10,000 applications	1.5	[0.9, 2.4]
		>10,000 applications	1.8	[1.0, 3.0]

406 \* aOR: adjusted odds ratio

407 \*\* 10,000 applications are equivalent to daily use for 30 year

#### 4. Discussion

The present analysis of the association between perineal use of talc powder and ovarian cancer risk considered four decades of scientific work exploring the epidemiological associations and non-human studies. The motivation for this review is based on two questions: what do human epidemiology studies of perineal talc exposure reveal about potential ovarian carcinogenicity, and what do in-vitro and in-vivo studies suggest about potential mechanisms of toxicity?

A systematic review of the human epidemiology studies was conducted to address the first question. Thirty observational epidemiologic studies were identified and assessed for quality using the NOS [6]. In parallel with the review of human epidemiological evidence, a (non-systematic) review of evidence exploring in vitro and in vivo toxicology data on talc was conducted to explore how talc might produce biological changes. This latter review provides some insights concerning possible mechanisms of talc toxicity, including oxidative stress, immune system alterations and inflammatory responses. However, it also indicates that talc is not genotoxic. In total, the epidemiology studies suggest that perineal exposure to talc powder is a possible human ovarian carcinogen but there are concerns that the actual exposure experienced by these women over the past 40-50 years is not well understood. As reported by Langesth and colleagues [67], there had been some concern that asbestos-contaminated talc powder that was produced prior to 1976 might have been a confounder; however, the similarity of findings between studies published prior to and after this point suggests asbestos contamination does not explain the positive association between perineal use of talc powder and risk of ovarian cancer [25, 27].

Human observational studies have inherent limitations that could bias the findings. Potentially important sources of bias reported in the included studies include: 1) selection bias due to low response rates from cases and controls or from limiting subjects to English-speaking women of two specific races, and 2) exposure misclassification due to recall bias inherent in case control studies. Other limitations included small sample sizes in some studies, small numbers of subjects in subgroup analyses, lack of information on duration of talc use in many studies that only compared ever vs never users, as well as lack of information on the talc content of the different brands of genital powders used. In two of the three cohort studies, the follow-up period between exposure assessment and end of study could have been inadequate to detect a potential association between talc exposure and ovarian cancer. Houghton et al. [39] reported a mean follow up of 12.4 years, while Gates et al. [36] followed a cohort of women for 24 years. However, Gertig et al. [37] and Gonzalez et al. [38] noted that one of their main limitations is the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer. For example, studies of smoking and ovarian cancer suggest that follow-up periods as long as four decades improve recognition of the carcinogenic effects of smoking [72]; longer follow up periods may also improve characterization of the association between talc and ovarian cancer. In this regard, the minimum latency period for radiation-induced ovarian cancer among Hiroshima atomic bomb survivors has been reported to range from 15 to 20 years [73, 74]. Common strengths reported in most studies were the selection of population controls in many of the case control studies and having relatively large sample sizes that allowed a multitude of stratified analyses.

Effect estimates in this meta-analysis were pooled from 24 case control studies and 3 cohort studies, and refer to ever vs never use of perineal talc. Pooling by study design showed a notably higher risk estimate for case-control [OR: 1.32 (95% CI: 1.24 to 1.40),  $P < 0.00001$ ,  $I^2 = 22\%$ ] compared to cohort studies [OR: 1.06 (95% CI: 0.9 to 1.25),  $P = 0.49$ ,  $I^2 = 17\%$ ]. Although the reasons for this are unclear, the difference could potentially be due to issues relating to latency, study power, or exposure misclassification.

Although cohort study designs are efficient for examining diseases with a long latency period, it is essential that the period between talc exposure and the cancer diagnosis be sufficiently long. Gonzalez et al. [38] suggested that the latency period for ovarian cancer is between 15 to 20 years. In the cohort studies included in this review, Houghton et al. [39] reported a mean follow up of 12.4 years while Gates et al. [36] followed a cohort of women for 24 years. Gertig et al. [37] and Gonzalez et al. [38] noted that one of their studies' main limitations was the relatively short follow up periods that may not be adequate to detect a potential association between talc exposure and ovarian cancer.

In addition, cohort studies included may have been underpowered to detect an odds ratio (relative risk) of 1.3 estimated from the case control studies. This was noted by Narod et al. [75], who suggest that cohorts of at least 200,000 women would be needed to reach statistical significance if the true odds ratio is 1.3. The cohort studies included in this review included much smaller cohort sizes, ranging between 41,654 and 78,630 women.

Finally, in cohort studies, talc exposure was assessed at cohort entry and was used as a measure of chronic talc use during follow up. It is possible that women who were not exposed to perineal talc at the time of cohort entry began using talc at a later time, and vice versa, possibly introducing non-differential misclassification of exposure, which could bias the risk estimate towards the null value of unity. Conversely, in the presence of differential exposure misclassification, a bias away from the null hypothesis could accentuate differences between the cohort and case-control studies.

#### **4.1. Exposures and outcomes**

All epidemiological studies included in our review evaluated the association between the perineal application of talc and subsequent diagnosis of ovarian cancer. Perineal vs body exposure is an important distinction, as the movement of talc is thought to follow an ascending path from the perineum through the vagina, uterus and fallopian tubes to the ovarian (as well as fallopian tube and peritoneal) epithelium.

Ovarian cancer is a common gynecologic malignancy in developed and developing countries. Risk factors for ovarian cancer include age, infertility, nulligravidity, endometriosis, hereditary ovarian cancer, tobacco and asbestos.

Protective factors for ovarian cancer include oral contraceptives, bilateral tubal ligation, salpingo-oophorectomy, hysterectomy, and breast feeding [76]. It is a difficult cancer to diagnose early, with approximately 60% of the individuals diagnosed after the cancer has metastasized from the pelvic region, where this cancer begins. In the meta-analysis, comparing ovarian cancer risk among women who used talc versus those who



never used talc (using both case-control and cohort designs), we observed an approximate 30% increase in ovarian cancer risk in the group who used talc. The most common type of ovarian cancer seen in the general population, and among the women exposed to talc were of epithelial origin, most common histologic type (accounting for about 95% of all cases in the general population), and of serous morphology, the most common subtype (comprising about 75% in the general population).

The cell-type of origin and morphology of talc induced ovarian cancer is similar to that observed in typical ovarian cancer with approximately 95% derived from epithelium (from fallopian tube fimbriae, ovarian or peritoneal) with serous tumors as the most common subtype. Like most ovarian cancers, those associated with talc exposure are typically diagnosed late in the course of the disease (~60% are diagnosed after the disease has spread outside of the pelvis). This late diagnosis complicates our understanding of the history and origin of the disease.

Demographic factors were analyzed using subgroup analysis where possible, and these were generally consistent with what has been previously observed with respect to ethnicity and risk of ovarian cancer. Additionally, these data also provide support for a mechanism of ovarian cancer induction working via an inflammatory pathway associated with oxidative stress [27, 77, 78].

A small number of studies explored the issue of ethnicity: Asians (1 study), Hispanics (2 studies), and African-Americans and Whites (3 studies each). Among these studies the risk for talc associated ovarian cancer was 1.70 (Hispanics), 1.67 (African Americans), 1.28 (Whites) and 0.04 (Asians). These risk factors compare with the demographics of ovarian cancer in the US population with an overall prevalence of

ovarian cancer of 12.7/100,000 among Whites 13.4/100,00, Hispanics 11.3/100,000, African Americans 9.8/100,000, and Asians 9.8/100,000. The difference in US prevalence and risk of talc induced ovarian cancer among Hispanics and African Americans may provide further evidence concerning exposures or mechanism of action [76].

A variety of factors were assessed with respect to the studies contributing to the meta-analysis, including study quality (NOS) and publication year. In general, the risk of talc associated ovarian cancer was similar among studies with an NOS  $\geq 7$  or NOS  $< 7$ . Year of publication also failed to demonstrate a significant impact on reported talc risk estimates.

## **4.2. Exposure metrics**

Given that the epidemiological studies indicate that talc is a possible human carcinogen, we next evaluated the studies to identify those comparing differences in exposure. The initial assessment exploring frequency of use, utilized a qualitative exposure metric: low, medium and high. Ovarian cancer was observed to increase between the medium and high exposure groups, consistent with an exposure-response relationship. Several studies explored duration of use (years) and risk of ovarian cancer; 20+ years (2 studies), 10 (5 studies), 10/20 (2 studies), and observed that the risk was greatest in the 20+ year exposure group, followed by lower risk in the 10/20 year and <10-year exposure groups.

Several studies explored the route of exposure or approach to talc application on ovarian cancer risk, including; hysterectomy, bilateral tubal ligation, diaphragm,

underwear, sanitary napkin, as these can provide insight into differences in exposure of the fallopian tube, ovarian and peritoneal epithelium. Use of a diaphragm, as well as tubal ligation act to interrupt exposure of perineal talc to reproductive tract. In contrast, application to underwear and sanitary napkin exposure will provide broader exposures. As hypothesized, the use of diaphragm and bilateral tubal ligation decreased ovarian cancer risk [22].

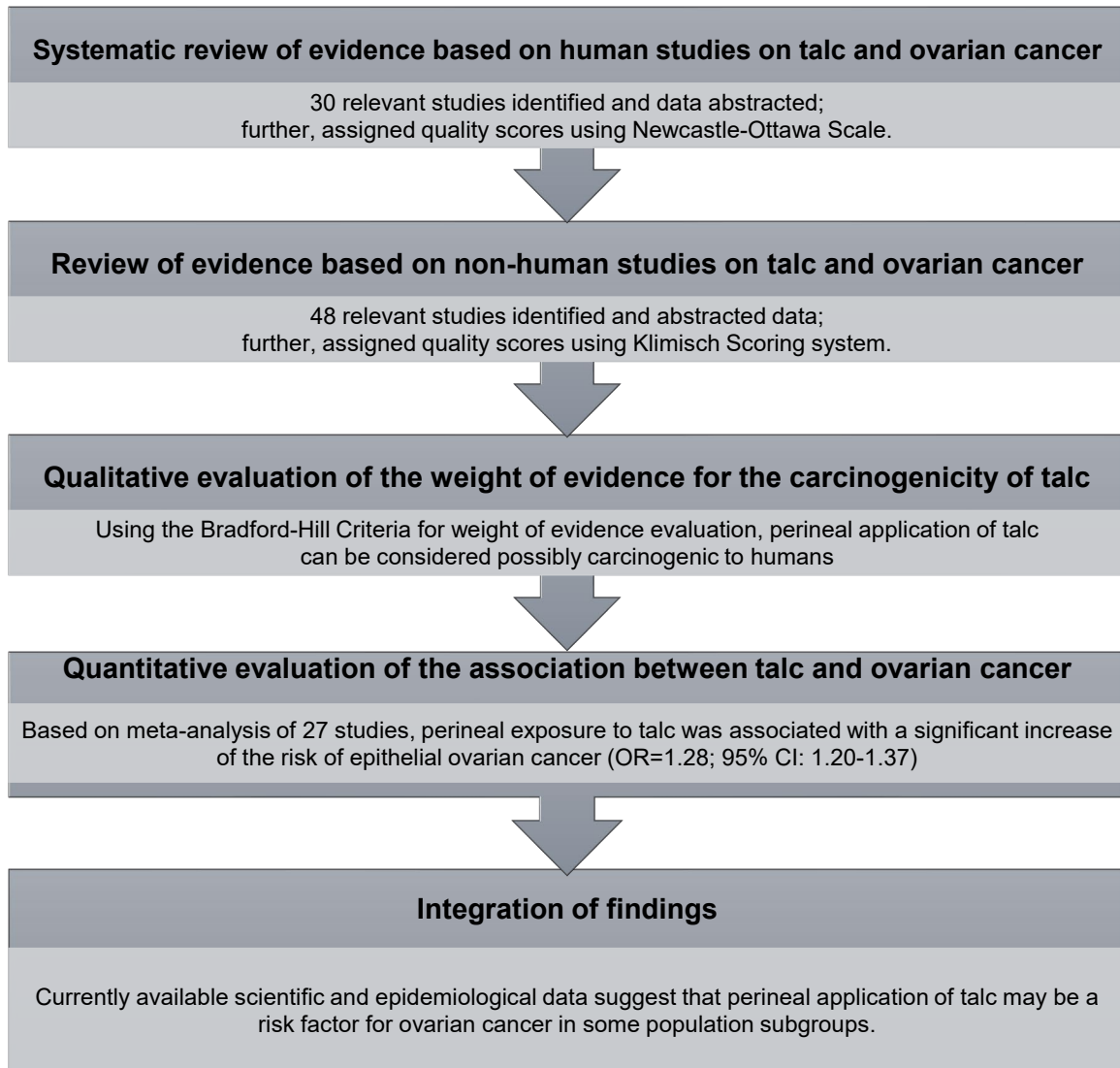
### **4.3. Modifying Factors**

Modifiers of the risk of ovarian cancer, either associated with talc exposure, or a spontaneous disease, can provide clues to potential mechanisms of causation. Menopausal status and use of hormones can modify the risk for ovarian cancer. For example, among post-menopausal women receiving hormonal therapy the risk for ovarian cancer is greater than those who are premenopausal and those who are post-menopausal not receiving hormone therapy. It has also been observed that women receiving fertility treatment who do not become pregnant are at greater risk for ovarian cancer [22]. These data suggest that hormonal status (elevated estrogens and/or gonadotropins) plays a role in the mechanism of action of talc associated ovarian cancer.

Subgroup analyses in the meta-analysis indicated that interruption of the pathway from perineum to pelvis (as with bilateral tubal ligation or use of diaphragm) decreased risk for ovarian cancer. This supports the hypothesis that talc acts by local action on the ovary. Given the data developed in non-human studies suggesting an inflammatory response of epithelial cells to talc, and histological observations

567 corroborating those observations, additional support for an inflammatory pathway  
568 leading to ovarian cancer is provided. One study recently explored the use of anti-  
569 inflammatory drugs and observed a decreased risk for ovarian cancer, also supporting  
570 the importance of an inflammatory pathway with oxidative stress [77].

571



572

573 **Figure 4: Detailed process flow for assessment of talc carcinogenicity**

574

## **5. Conclusion**

We conducted an extensive search, examination, assessment and analysis of evidence from published human and non-human original as well as all published reviews that considered the association between genital/perineal use of talc powder and risk of ovarian cancer. The steps followed in conducting this review are summarized in Figure 4, along with the key findings at each step. Consistent with previous evaluations the IARC in 2010 [2], and subsequent evaluations by individual investigators [3, 5, 69], the present comprehensive evaluation of all currently available relevant data indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans.

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# Exhibit 64

1                   IN THE UNITED STATES DISTRICT COURT  
2                   FOR THE DISTRICT OF NEW JERSEY  
3  
4                   \_\_\_\_\_  
5                   ) )  
6                   IN RE: JOHNSON & JOHNSON TALCUM )  
7                   POWDER PRODUCTS MARKETING, SALES )  
8                   PRACTICES, AND PRODUCTS LIABILITY )  
9                   LITIGATION )  
10                   ) MDL No.  
11                   ) 2738 (FLW)(LHG)  
12                   )  
13                   \_\_\_\_\_) )

12                   VIDEOTAPED DEPOSITION OF  
13                   REBECCA SMITH-BINDMAN, M.D.  
14                   San Francisco, California  
15                   Thursday, February 7, 2019  
16                   Volume I

23                   Reported by:  
24                   MARY J. GOFF  
25                   CSR No. 13427

<p style="text-align: right;">Page 2</p> <p>1 2 3 4 5 Videotaped Deposition of REBECCA 6 SMITH-BINDMAN, M.D., Volume I, taken on behalf of 7 Johnson &amp; Johnson, at Levin Simes Abrams LLP, 8 1700 Montgomery Street, Suite 250, San Francisco, 9 California 94111, beginning at 9:20 a.m. and ending 10 at 4:01 p.m., on February 7, 2019, before MARY J. 11 GOFF, California Certified Shorthand Reporter No. 12 13427. 13 14 15 16 17 18 19 20 21 22 23 24 25</p>	<p style="text-align: right;">Page 4</p> <p>1 APPEARANCES (continued): 2 For Plaintiffs 3 Restaino Law LLC 4 BY: JOHN M. RESTAINO JUNIOR 5 Attorney at Law 6 130 Forest Street 7 Denver, Colorado 80220 8 jrestaino@restainollc.com 9 720-891-7921 10 11 12 For Defendant Johnson &amp; Johnson 13 Tucker Ellis LLP 14 BY: MICHAEL C. ZELLERS 15 Attorney at Law 16 515 South Flower Street 17 42nd Floor 18 Los Angeles, California 90071 19 michael.zellers@tuckerellis.com 20 213-430-3301 21 22 23 24 25</p>
<p style="text-align: right;">Page 3</p> <p>1 APPEARANCES: 2 3 For Plaintiffs 4 Beasley Allen Law Firm 5 BY: P. LEIGH O'DELL 6 MARGARET M. THOMPSON, MD, JD, MPAff 7 Attorney at Law 8 218 Commerce Street 9 Montgomery, Alabama 36103 10 leigh.odell@beasleyallen.com 11 334-269-2343 12 For Plaintiffs 13 Robinson Calcagnie, Inc. 14 BY: CYNTHIA L. GARBER 15 Attorney at Law 16 19 Corporate Plaza Drive 17 Newport Beach, California 92660 18 cgarber@robinsonfirm.com 19 For Plaintiffs 20 Wilentz, Goldman &amp; Spitzer P.A. 21 Daniel R. Lapinski 22 Attorney at Law 23 90 Woodbridge Center Drive, 24 Suite 900 Box 10 25 Woodbridge, New Jersey 07095-0958</p>	<p style="text-align: right;">Page 5</p> <p>1 APPEARANCES (continued): 2 For Defendant Johnson &amp; Johnson 3 Skadden, Arps, Slate, Meagher &amp; Flom, LLP. 4 BY: BENJAMIN HALPERIN 5 Attorney at Law 6 4 Times Square 7 New York, New York 10036 8 benjamin.halperin@skadden.com 9 212-735-2453 10 11 12 For Defendant Imerys 13 Dykema 14 BY: JANE BOCKUS 15 Attorney at Law 16 112 E. Pecan Street 17 Suite 1800 18 San Antonio, Texas 78205 19 jbockus@dykema.com 20 210-554-5549 21 22 23 24 25</p>

<p style="text-align: right;">Page 6</p> <p>1 APPEARANCES (continued):</p> <p>2 For Defendant Imerys</p> <p>3 Gordon &amp; Rees LLP</p> <p>4 BY: JENNIFER A. FOSTER</p> <p>5 Attorney at Law</p> <p>6 816 Congress Avenue</p> <p>7 Suite 1510</p> <p>8 Austin, Texas 78701</p> <p>9 jfooster@gordonrees.com</p> <p>10 512-391-0197</p> <p>11</p> <p>12</p> <p>13 For Defendant PCPC, Personal Care Products Council</p> <p>14 Seyfarth Shaw, LLP</p> <p>15 BY: JAMES R. BILLINGS-KANG</p> <p>16 Attorney at Law</p> <p>17 975 F Street, NW</p> <p>18 Washington, D.C. 20004</p> <p>19 jbillingskang@seyfarth.com</p> <p>20 202-828-5356</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 8</p> <p>1 INDEX</p> <p>2 WITNESS EXAMINATION</p> <p>3 REBECCA SMITH-BINDMAN, M.D.</p> <p>4 Volume I</p> <p>5</p> <p>6 BY MR. ZELLERS 12</p> <p>7</p> <p>8 NUMBER DESCRIPTION PAGE</p> <p>9 Exhibit 1 Notice of Oral and Videotaped Deposition 24</p> <p>10</p> <p>11 Exhibit 2 Rule 26 Expert Report of Rebecca Smith-Bindman, MD 25</p> <p>12</p> <p>13 Exhibit 3 IMERYS list, Amended Expert Report 30</p> <p>14</p> <p>15 (Exhibit 4-11, premarked Hopkins Exhibit 28</p> <p>16 (Spreadsheet) premarked Pier 47 (Exhibit Number</p> <p>17 list) and unmarked article "Pycnogenol Reduces</p> <p>18 Talc-induced Neoplastic Transformation in Human</p> <p>19 Ovarian Cell Cultures" (Pltf_MISC_00000046) are</p> <p>20 contained in the blue folder)</p> <p>21</p> <p>22 Exhibit 4 Reproductive Sciences 34</p> <p>23</p> <p>24 Exhibit 5 Safety Assessment article 35</p> <p>25</p>
<p style="text-align: right;">Page 7</p> <p>1 APPEARANCES (continued):</p> <p>2</p> <p>3 For Defendants PTI Union, LLC and PTI Royston, LLC</p> <p>4 Tucker Ellis LLP</p> <p>5 BY: CAROLINE M. TINSLEY</p> <p>6 Attorney at Law</p> <p>7 100 South 4th Street</p> <p>8 Suite 600</p> <p>9 St. Louis, Missouri, 63102</p> <p>10 caroline.tinsley@tuckerellis.com</p> <p>11</p> <p>12 Videographer:</p> <p>13 Joseph Morgas</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>	<p style="text-align: right;">Page 9</p> <p>1 EXHIBITS CONTINUED: PAGE</p> <p>2 Exhibit 6 IARC Monographs, Volume 93 35</p> <p>3</p> <p>4 Exhibit 7 J&amp;J article by Owen Dyer, BMJ 36</p> <p>5</p> <p>6 Exhibit 8 IARC Volumes 1-123 36</p> <p>7</p> <p>8 Exhibit 9 "On Talc Translocation from the Vagina" article 36</p> <p>9</p> <p>10 Exhibit 10 Alterations in Gene Expression article 37</p> <p>11</p> <p>12 Exhibit 11 Draft Screening Assessment, 12/18 38</p> <p>13</p> <p>14 Exhibit 12 (Binder) Talc Articles I 39</p> <p>15</p> <p>16 Exhibit 13 (Binder) Talc Articles II 39</p> <p>17 (Exhibit 21 is inside Exhibit 13)</p> <p>18 Exhibit 14 CV of Smith-Bindman, MD 53</p> <p>19 Exhibit 15 List of articles 54</p> <p>20 Exhibit 16 9/24/18 e-mail string forest plots 76</p> <p>21</p> <p>22 Exhibit 17 Rule 26 Expert Report of Smith-Bindman, MD 90</p> <p>23</p> <p>24 Exhibit 18 The Association Between Talc Use and Ovarian Cancer article 95</p> <p>25</p>

Rebecca Smith-Bindman, M.D.

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<p style="text-align: right;">Page 11</p> <p>1 San Francisco, California</p> <p>2 February 7, 2019</p> <p>3 9:20 a.m.</p> <p>4</p> <p>5 REBECCA SMITH-BINDMAN, M.D.,</p> <p>6 being first duly sworn or affirmed to testify to the</p> <p>7 truth, the whole truth, and nothing but the truth,</p> <p>8 was examined and testified as follows:</p> <p>9 THE VIDEOGRAPHER: We are now on the</p> <p>10 record. My name is Joseph morgue. I'm a</p> <p>11 videographer for Golkow Litigation Services.</p> <p>12 Today's date is February 7, 2019. The</p> <p>13 time on the video monitor is 9:20 a.m.</p> <p>14 This video deposition is being held at</p> <p>15 1700 Montgomery Street, Suite 250, San Francisco,</p> <p>16 California, in the matter In Re: Johnson &amp; Johnson</p> <p>17 Talcum Powder Products Marketing, Sales Practices,</p> <p>18 and Products Liability Litigation, for the United</p> <p>19 States District Court, for the District of</p> <p>20 New Jersey.</p> <p>21 The deponent is Dr. Rebecca Smith-Bindman.</p> <p>22 Counsel will be noted on the stenographic record.</p> <p>23 The court reporter is Mary Goff. She will now</p> <p>24 administer the oath.</p> <p>25</p>	<p style="text-align: right;">Page 13</p> <p>1 understand, please don't answer it. Tell us you</p> <p>2 don't understand, and we'll rephrase the question or</p> <p>3 repeat it so it's clear to you.</p> <p>4 Can you do that?</p> <p>5 A I can.</p> <p>6 Q If you answer a question, is it fair for</p> <p>7 us to assume that you understood it?</p> <p>8 A It is.</p> <p>9 Q Please don't guess or speculate as to any</p> <p>10 answers. If you don't know the answer to a question</p> <p>11 or it would call you to guess or speculate, tell us.</p> <p>12 Can you do that?</p> <p>13 A I can.</p> <p>14 Q If at any time you need to take a break as</p> <p>15 we proceed through the day, please tell us. And</p> <p>16 once we finish whatever line of questioning we're</p> <p>17 involved with, then we will take a break.</p> <p>18 A Okay.</p> <p>19 Q Tell us the times that you have been</p> <p>20 deposed. When is the last time you were deposed?</p> <p>21 A I think approximately six years ago.</p> <p>22 Q What was the litigation or the matter?</p> <p>23 A I have been deposed a few times. I'm not</p> <p>24 sure which happened when --</p> <p>25 Q That's fine.</p>

<p style="text-align: right;">Page 14</p> <p>1 A -- but I can tell you in general what they 2 were about.</p> <p>3 Q Tell us -- the three to four times that 4 you have been deposed, will you tell us what each of 5 those matters was?</p> <p>6 A Yes. I am in addition to being an 7 epidemiologist, I'm a clinical radiologist. And 8 each of those cases had to do with diagnosis and 9 communication within medical malpractice cases.</p> <p>10 One case had to do with a delayed 11 diagnosis of breast cancer and not communicating 12 results.</p> <p>13 One case had to do with a misdiagnosis of 14 a first trimester pregnancy loss.</p> <p>15 One case had to do with misdiagnosis of a 16 complication of a twin/twin pregnancy. I think 17 those are the cases I was deposed in.</p> <p>18 Q All of the cases in which you have been 19 deposed previously have been medical malpractice 20 cases?</p> <p>21 A Yes.</p> <p>22 Q Were those cases in which you had provided 23 treatment to a patient or were they cases in which 24 you were an expert witness independent of that 25 particular plaintiff?</p>	<p style="text-align: right;">Page 16</p> <p>1 A And -- and I was deposed.</p> <p>2 MS. O'DELL: Excuse me.</p> <p>3 Q (BY MR. ZELLERS) Yes. So three prior 4 litigations in which you served as an expert and you 5 were deposed; is that right?</p> <p>6 A I --</p> <p>7 MS. O'DELL: Object to the form. I think 8 she said four, but --</p> <p>9 MR. ZELLERS: Well, she said three to 10 four. But then when she was telling us about those 11 cases --</p> <p>12 A -- so I remember what was fourth case was.</p> <p>13 Q (BY MR. ZELLERS) All right. What was the 14 fourth case?</p> <p>15 A There was a case of delay in the diagnosis 16 of an ovarian cancer.</p> <p>17 Q Where was that case?</p> <p>18 A Somewhere in the middle of the country.</p> <p>19 Q When did you testify in that case?</p> <p>20 A I -- I only testified in a single case. 21 So it -- do you mean deposed?</p> <p>22 Q Yes. When were you deposed in that case?</p> <p>23 A I -- sometime between -- all of the cases 24 were sometime between six and 12 years ago. I'm 25 not --</p>
<p style="text-align: right;">Page 15</p> <p>1 A For each of those cases, I was an expert 2 witness. I had never personally been involved in a 3 medical malpractice cases.</p> <p>4 Q Were each of those cases in the 5 San Francisco area or where were they located?</p> <p>6 A None of those cases were in the 7 San Francisco area. One of them was in Huntsville 8 Alabama, one was in Northern California, and one was 9 in Southern California.</p> <p>10 Q Do you remember the names of any of those 11 cases?</p> <p>12 A I do not.</p> <p>13 Q Do you remember the name of the lawyer or 14 lawyers that you worked with in those cases?</p> <p>15 A I do not.</p> <p>16 Q Did you testify in those cases on behalf 17 of the plaintiff or on behalf of a defendant?</p> <p>18 A They were split. So I have been involved 19 in cases on both sides.</p> <p>20 Q Well, my understanding is you have been 21 involved in three prior litigations; is that right 22 --</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 Q (BY MR. ZELLERS) -- in which you served as 25 an expert witness and were deposed?</p>	<p style="text-align: right;">Page 17</p> <p>1 Q All right. Did --</p> <p>2 A -- sure I remember the years.</p> <p>3 Q The case in which you testified as an 4 expert witness in the delay of diagnosis of ovarian 5 cancer, were you testifying for the defense or for 6 the plaintiff?</p> <p>7 A I believe that case was for the defense.</p> <p>8 Q Do you remember the name of the plaintiff?</p> <p>9 A I do not.</p> <p>10 Q Do you remember the name of the defendant?</p> <p>11 A I do not.</p> <p>12 Q Do you remember the name of the attorney 13 who retained you?</p> <p>14 A I do not.</p> <p>15 Q Do you remember where in the middle of the 16 country that case was pending?</p> <p>17 A I do not.</p> <p>18 Q You stated that you have testified one 19 time at trial; is that right?</p> <p>20 A Yes.</p> <p>21 Q Where did you testify at trial?</p> <p>22 A That was Huntsville -- the Fayetteville, 23 Alabama case.</p> <p>24 Q In that case, did you testify for the 25 plaintiff or the defense?</p>



<p style="text-align: right;">Page 18</p> <p>1 A For the plaintiff.</p> <p>2 Q Do you remember how long ago it was?</p> <p>3 A In the ballpark of seven or eight years</p> <p>4 ago.</p> <p>5 Q The Northern California case that you gave</p> <p>6 deposition testimony in that -- in, was that for the</p> <p>7 plaintiff or the defense?</p> <p>8 A I don't remember.</p> <p>9 Q Southern California, that medical</p> <p>10 malpractice case, did you testify for the plaintiff</p> <p>11 or the defense?</p> <p>12 A Can I go back? I -- I do remember.</p> <p>13 So the Northern California case was the</p> <p>14 plaintiff. The Southern California case was the</p> <p>15 defense.</p> <p>16 Q Do you remember the attorneys that you</p> <p>17 worked with in the Northern California case?</p> <p>18 A I do not.</p> <p>19 Q The Southern California case?</p> <p>20 A I do not.</p> <p>21 Q Do you remember the name of any of the</p> <p>22 parties in any of the cases in which you have either</p> <p>23 given deposition testimony in or trial testimony in?</p> <p>24 A I do not.</p> <p>25 Q Today I'm going to ask you questions about</p>	<p style="text-align: right;">Page 20</p> <p>1 A Yes.</p> <p>2 Q You are not testifying here today as a</p> <p>3 radiologist; is that right?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A I think some of my experiences as a</p> <p>6 radiologist are highly relevant to my expertise, and</p> <p>7 so there are some questions that I think that that</p> <p>8 is very relevant.</p> <p>9 Q (BY MR. ZELLERS) Are there any areas in</p> <p>10 which you anticipate providing expert testimony in</p> <p>11 this litigation, other than in the areas of</p> <p>12 epidemiology and radiology?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A I mentioned ovarian cancer. So risk</p> <p>15 factors for ovarian cancer falls into epidemiology.</p> <p>16 The mechanism of ovarian cancer, the</p> <p>17 pathophysiology, the biological processes are not</p> <p>18 technically epidemiology. They're related, and so</p> <p>19 some of my opinions, I think, would fall into that</p> <p>20 category.</p> <p>21 Q (BY MR. ZELLERS) How would you define that</p> <p>22 area of expertise for which you are providing expert</p> <p>23 opinions?</p> <p>24 MS. O'DELL: Object to the form.</p> <p>25 Q (BY MR. ZELLERS) We have got that you are</p>
<p style="text-align: right;">Page 19</p> <p>1 talcum powder or baby powder. Can we agree that</p> <p>2 when I refer during the deposition to products, to</p> <p>3 talc products, talcum powder products, baby powder,</p> <p>4 or Shower to Shower at issue in this MDL, that I am</p> <p>5 referring to the baby powder product manufactured by</p> <p>6 Johnson &amp; Johnson Consumer Products, Inc., and the</p> <p>7 Shower to Shower product that was formerly</p> <p>8 manufactured by Johnson &amp; Johnson Consumer Products,</p> <p>9 Inc.?</p> <p>10 A Yes.</p> <p>11 Q How would you define the area of expertise</p> <p>12 in which you were offering opinions in this case,</p> <p>13 "this case" being the talc MDL?</p> <p>14 A I was asked to provide an expert review in</p> <p>15 the area of epidemiology, ovarian cancer and its</p> <p>16 causes, the health effects of talc powder products.</p> <p>17 I think those are the main areas.</p> <p>18 Q Are -- are you testifying today as an</p> <p>19 epidemiologist?</p> <p>20 A Yes.</p> <p>21 MS. O'DELL: Object to --</p> <p>22 A Am --</p> <p>23 MS. O'DELL: -- the form.</p> <p>24 A -- I bringing expertise to that?</p> <p>25 Q (BY MR. ZELLERS) Yes.</p>	<p style="text-align: right;">Page 21</p> <p>1 going to provide expert opinions relating to</p> <p>2 epidemiology. You're going to provide expert</p> <p>3 opinions relating to radiology.</p> <p>4 Are there any other areas that you intend</p> <p>5 to provide expert opinions in?</p> <p>6 MS. O'DELL: Other than what she has just</p> <p>7 described?</p> <p>8 Q (BY MR. ZELLERS) Well, other than</p> <p>9 epidemiology and radiology.</p> <p>10 MS. O'DELL: Object to the form. She gave</p> <p>11 another -- a host -- a suite of things she expected</p> <p>12 to testify on, but --</p> <p>13 MR. ZELLERS: And so --</p> <p>14 MS. O'DELL: -- I'll object to the form.</p> <p>15 MR. ZELLERS: -- yeah, thank you.</p> <p>16 A Could you repeat back to me what I have</p> <p>17 already said?</p> <p>18 Q (BY MR. ZELLERS) No. I'm asking you what</p> <p>19 you are going to provide expert testimony in, what</p> <p>20 you consider yourself to be an expert in.</p> <p>21 I understand epidemiology, and I</p> <p>22 understand the epidemiology opinions you are going</p> <p>23 to give, relate to whether or not talcum powder is</p> <p>24 associated with ovarian cancer, whether or not</p> <p>25 talcum powder causes ovarian cancer, so I believe</p>

<p style="text-align: right;">Page 22</p> <p>1 those are epidemiology-based opinions.  2 I also understand that you have a -- your  3 training and your background is in radiology and  4 that you will provide, to the extent relevant,  5 radiology opinions.  6 But you're not testifying here today as a  7 gynecologic oncologist, are you?  8 A I am not.  9 Q You are not testifying here today as an  10 expert in asbestos; is that fair?  11 MS. O'DELL: Object to the form.  12 A I am going to provide opinions, if asked,  13 about the health effects of asbestos.  14 Q (BY MR. ZELLERS) Are you an expert or do  15 you consider yourself to be an expert in asbestos?  16 MS. O'DELL: Object to the form.  17 A The question is about asbestos, in  18 general, and I consider myself an expert on the  19 health effects of asbestos.  20 Q (BY MR. ZELLERS) Does that mean that you  21 are an expert in asbestos or simply looking at  22 studies that have evaluated the epidemiology of  23 asbestos and asbestos exposure to certain  24 conditions?  25 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 24</p> <p>1 Q -- not an expert -- well -- and let me  2 withdraw that.  3 You have produced an expert report in this  4 case; is that right?  5 A I have.  6 Q Let's mark a couple of things at the  7 outset.  8 Deposition Exhibit 1 is copy of the Notice  9 of Deposition.  10 (Exhibit 1 was marked for identification  11 and is attached to the transcript.)  12 MS. O'DELL: Thank you.  13 Q (BY MR. ZELLERS) Have you seen the Notice  14 of Deposition prior to today?  15 A Yes, I have.  16 Q Have you either brought with you or  17 through counsel have they brought all of the  18 materials that you believe are responsive to the  19 Deposition Notice?  20 MR. ZELLERS: And, Ms. O'Dell, I recognize  21 that you have objected to the Deposition Notice and  22 the record will reflect that.  23 MS. O'DELL: And just so I have a chance  24 to say something, we'll just reassert those  25 objections now.</p>
<p style="text-align: right;">Page 23</p> <p>1 A I think there are a lot of acts -- aspects  2 of asbestos, so I would absolutely not consider  3 myself an expert on the geology of asbestos or in  4 the mechanism of mining asbestos.  5 But I would consider myself an expert on  6 the changes to the body that can be the result of  7 exposure to asbestos in the context of epidemiology  8 studies, but also in the context of molecular  9 changes, cellular changes like that.  10 And -- and those technically are probably  11 not in the category of epidemiology, but would  12 overlap other areas of my training and experience,  13 such as pathology and...  14 Q You are not an expert in the testing of  15 asbestos; is that fair?  16 A I -- I would, yes, agree.  17 Q You are not an expert in the different  18 forms and types of asbestos --  19 A I --  20 Q -- correct?  21 A -- I -- correct.  22 Q Okay.  23 A I'm not an expert in those types of --  24 Q You are --  25 A -- asbestos.</p>	<p style="text-align: right;">Page 25</p> <p>1 Dr. Smith-Bindman has brought with her  2 documents subject to our objections.  3 MR. ZELLERS: And I would really like  4 Dr. Smith-Bindman to answer the question.  5 MS. O'DELL: I'm sure she's ready to do  6 that.  7 A To the best of my knowledge, I have  8 responded or brought or provided all of --  9 Q (BY MR. ZELLERS) You --  10 A -- those items.  11 Q -- you are not aware of items that are  12 called for in the Deposition Notice, what we have  13 marked as Exhibit 1 that have not been produced or  14 not available here today; is that right?  15 A That's correct.  16 Q Ms. O'Dell and I spoke earlier about your  17 invoices, and apparently you do have some invoices  18 relating to your work in this matter. At some point  19 today we'll collect those and we will mark those.  20 (Exhibit 2 was marked for identification  21 and is attached to the transcript.)  22 Q (BY MR. ZELLERS) Deposition Exhibit 2 is  23 your report in this matter; is that right?  24 MS. O'DELL: Thank you.  25 A Okay. Yes.</p>

<p style="text-align: right;">Page 26</p> <p>1 Q (BY MR. ZELLERS) Does your report in this                  2 matter, Deposition Exhibit 2, contain all of the                  3 opinions that you intend to offer at trial or at any                  4 hearing in this matter?                  5 A The report summarizes my opinions. I have                  6 written in the report. As new information comes                  7 available, I may take that into account as well.                  8 So when we began, counsel mentioned a few                  9 additional papers that I had seen since the time my                  10 report was written. And so those are -- are --                  11 won't -- have not changed my views, but those are                  12 not necessarily referenced in this report.                  13 Q In terms of your opinions and the opinions                  14 that you expect to render in this matter, either at                  15 trial or any hearing, those opinions are contained                  16 in your report which we marked as Exhibit 2,                  17 correct?                  18 MS. O'DELL: Object to the form.                  19 A I have not, since writing my report, seen                  20 any documents that have changed my opinions.                  21 But as I continue to keep up with the                  22 published literature, my opinions may reflect                  23 changing documents that I have seen since the time                  24 my report was generated.                  25</p>	<p style="text-align: right;">Page 28</p> <p>1 Q Okay. Right now all I want to do is get a                  2 list of what you have looked at and considered since                  3 you prepared your report.                  4 A I have seen an updated testing report by                  5 Mr. Longo.                  6 I have seen a report and deposition by                  7 Mr. Cooke. I -- I think those are the...                  8 Q You -- counsel for Plaintiffs, Ms. O'Dell,                  9 told me before the deposition that you also have                  10 looked at a health assessment from Health Canada or                  11 a risk assessment; is -- is that correct?                  12 A Yes, that's correct.                  13 Q All right. Did you also look at a                  14 meta-analysis that was performed or at least the                  15 draft of a meta-analysis by the first name, author,                  16 Thayer (phonetic)?                  17 A I -- I saw that report briefly.                  18 Q Anything else that you have reviewed                  19 and/or considered that is not included in the                  20 materials that you reference either in your list of                  21 references or in your Materials Considered List?                  22 A There was also a series of reports in --                  23 in The New York Times and Reuters and a summary of                  24 that in the BMJ, which I have seen since I have                  25 issued my report.</p>
<p style="text-align: right;">Page 27</p> <p>1 Q (BY MR. ZELLERS) All I can do is ask you                  2 questions today. As of today, does your report                  3 contain the opinions that you expect to provide at                  4 any trial or hearing in this matter?                  5 A Yes, they do.                  6 Q My understanding from one of your prior                  7 answers is that you have reviewed some additional                  8 materials since you prepared and signed your report                  9 on or about November 15 of 2018; is that right?                  10 A That is correct.                  11 Q Those materials, you believe, support the                  12 opinions that you have put in your report, but have                  13 not changed your opinions; is --                  14 A It --                  15 Q -- that right?                  16 A -- that's correct.                  17 Q What new or additional materials have you                  18 reviewed and considered since preparing your report                  19 on November 15, 2018?                  20 A So I have seen a draft of a publication --                  21 submitted for publication by Dr. Saed about the                  22 cellular and molecular changes to cell lines of                  23 being exposed to various talcum powder products,                  24 which I think is an important paper that has                  25 influenced my views.</p>	<p style="text-align: right;">Page 29</p> <p>1 Q Are you basing any of your opinions on the                  2 Reuters or New York Times articles?                  3 A Those reports support my opinions, but no,                  4 I'm not basing my report on -- on those.                  5 Q Ms. O'Dell also provided me with a list                  6 materials that she has represented that you have                  7 reviewed since you prepared your report.                  8 It's a series of Imerys documents. It's                  9 one J&amp;J produced document. And then the last item                  10 listed is an Amended Expert Report of Robert Cooke.                  11 Have you reviewed those materials since                  12 preparing your report?                  13 A So yes, the -- the Mr. Cooke report, which                  14 is one I mentioned. Yes, I have seen the Imerys                  15 report. And I can't remember what you said, the                  16 Johnson &amp; Johnson?                  17 Q Are those additional documents or                  18 materials that you have reviewed since preparing                  19 your report?                  20 A I'm sorry. I understand the question. I                  21 don't remember what the Johnson &amp; Johnson material                  22 was.                  23 Q I --                  24 A You listed it. I just don't --                  25 Q -- well, I didn't --</p>

<p style="text-align: right;">Page 30</p> <p>1 A -- remember that.</p> <p>2 Q -- list it. This was a list that was</p> <p>3 prepared and provided to me by counsel for</p> <p>4 Plaintiffs so --</p> <p>5 MS. O'DELL: But I don't think he</p> <p>6 characterized the documented in any way other than</p> <p>7 the Bates number, so -- so it's a J&amp;J document --</p> <p>8 A What is that item?</p> <p>9 MS. O'DELL: -- that's just the Bates</p> <p>10 number for that particular document. And it's</p> <p>11 the -- the test results that you reviewed yesterday.</p> <p>12 A Yes.</p> <p>13 (Exhibit 3 was marked for identification</p> <p>14 and is attached to the transcript.)</p> <p>15 Q (BY MR. ZELLERS) Are all of the documents</p> <p>16 contained on Exhibit 3, the -- a listing that was</p> <p>17 put together by counsel for the Plaintiffs,</p> <p>18 documents that you reviewed yesterday in preparation</p> <p>19 for your deposition today?</p> <p>20 A Yes.</p> <p>21 Q Are those documents that were selected by</p> <p>22 plaintiffs' counsel to show you to help prepare you</p> <p>23 for the deposition?</p> <p>24 MS. O'DELL: Object to the form.</p> <p>25 A The document are ones that I asked for to</p>	<p style="text-align: right;">Page 32</p> <p>1 is that right?</p> <p>2 A Yes, I did.</p> <p>3 MS. O'DELL: Object to the form.</p> <p>4 Q (BY MR. ZELLERS) You asked for documents</p> <p>5 that were both positive and negative relating that</p> <p>6 testing; is that right?</p> <p>7 A Yes.</p> <p>8 Q Do you believe that you have now seen, as</p> <p>9 part of your review, all documents relating to the</p> <p>10 testing of Johnson's baby powder and/or Shower to</p> <p>11 Shower powder?</p> <p>12 A I --</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A -- I do not believe I have seen the</p> <p>15 entirety of the testing results.</p> <p>16 Q (BY MR. ZELLERS) Was it your request that</p> <p>17 you see whatever pertinent documents that were</p> <p>18 relating to the testing of the baby powder?</p> <p>19 A It was not my request. I wanted to</p> <p>20 understand, in general, what kind of testing had</p> <p>21 been done. I -- I was not planning to delve into</p> <p>22 the entirety of testing.</p> <p>23 Q Any other materials that you have reviewed</p> <p>24 prior -- strike that -- subsequent to preparing your</p> <p>25 report, which we marked as Exhibit 2?</p>
<p style="text-align: right;">Page 31</p> <p>1 see testing results, both positive and negative,</p> <p>2 from Johnson &amp; Johnson. So I requested documents</p> <p>3 that would show that, and I believe that's what each</p> <p>4 of these were provided for.</p> <p>5 Q When did you make that request to</p> <p>6 plaintiffs' counsel?</p> <p>7 MS. O'DELL: And Mr. Zellers is -- he can</p> <p>8 ask you when you made the request. In terms of the</p> <p>9 specifics of the request or conversations with</p> <p>10 counsel, those would be protected, and I would</p> <p>11 instruct you not to -- to disclose those.</p> <p>12 A To not say when I read the request?</p> <p>13 MS. O'DELL: You can say when you gave the</p> <p>14 request. But the substance of the request or the</p> <p>15 substance of the discussions, I would have ask you</p> <p>16 not to --</p> <p>17 A Okay.</p> <p>18 MS. O'DELL: -- testify to those.</p> <p>19 Q (BY MR. ZELLERS) My question again is:</p> <p>20 When did you make the request for the documents that</p> <p>21 are identified on Exhibit 3?</p> <p>22 A I believe it was a few weeks ago.</p> <p>23 Q You made a request for testing documents</p> <p>24 of talcum powder used in Johnson &amp; Johnson Consumer,</p> <p>25 Inc., baby powder or former Shower to Shower powder;</p>	<p style="text-align: right;">Page 33</p> <p>1 A None that come to mind.</p> <p>2 Q You have brought with you here today</p> <p>3 several notebooks and it looks like a blue folder;</p> <p>4 is that right?</p> <p>5 A Yes.</p> <p>6 Q What is contained in the blue folder that</p> <p>7 you brought here today?</p> <p>8 A Primarily in the blue folder are either</p> <p>9 additional documents that I have reviewed since I</p> <p>10 wrote my report, but also a few documents that -- in</p> <p>11 preparation for the deposition, I went through my</p> <p>12 report and pulled some articles to look at in</p> <p>13 greater depth, and so I brought those with --</p> <p>14 Q So --</p> <p>15 A -- me.</p> <p>16 Q -- in the blue folder are materials that</p> <p>17 you pulled out to have available for the deposition</p> <p>18 today for your use as needed in responding to</p> <p>19 questions that were asked?</p> <p>20 A Yes, that's correct.</p> <p>21 Q Can I see you blue folder, please? And,</p> <p>22 Dr. Smith-Bindman, have you taken any medications</p> <p>23 that impair your ability to answer questions today?</p> <p>24 A I have not.</p> <p>25 Q All right. The first document in your</p>

<p style="text-align: right;">Page 34</p> <p>1 blue folder is a document, "Reproductive Sciences"</p> <p>2 at the top, "Molecular basis Supporting the</p> <p>3 Association of Talcum Powder Use with Increased Risk</p> <p>4 of Ovarian Cancer."</p> <p>5 The first named author is Nicole Fletcher.</p> <p>6 And is this the article by Dr. Saed that</p> <p>7 you sold me about?</p> <p>8 A Yes, it is.</p> <p>9 Q There are a number of notes and</p> <p>10 highlighting that are contained in the document.</p> <p>11 Are all of those your notes and highlighting?</p> <p>12 A They are.</p> <p>13 Q We'll mark your copy of Dr. Saed's paper</p> <p>14 as Exhibit 4.</p> <p>15 (Exhibit 4 was marked for identification</p> <p>16 and is attached to the transcript.)</p> <p>17 Q (BY MR. ZELLERS) The next paper in your</p> <p>18 blue folder that you brought here today is a</p> <p>19 document with the first named author, Fiume,</p> <p>20 F I U M E. The title is "Safety Assessment of Talc</p> <p>21 as Used in Cosmetics."</p> <p>22 It appeared in the International Journal</p> <p>23 of Toxicology. Again, there's highlighting in the</p> <p>24 document and underlying lining.</p> <p>25 Did you do the highlighting and did you do</p>	<p style="text-align: right;">Page 36</p> <p>1 Are those your notations?</p> <p>2 A Yes, they are.</p> <p>3 Q All right. We'll mark that as Exhibit 7.</p> <p>4 (Exhibit 7 was marked for identification</p> <p>5 and is attached to the transcript.)</p> <p>6 (Exhibit 8 was marked for identification</p> <p>7 and is attached to the transcript.)</p> <p>8 Q (BY MR. ZELLERS) Exhibit 8 are the</p> <p>9 classifications of the International Agency for</p> <p>10 Research on Cancer or IARC.</p> <p>11 Are you generally familiar with the IARC</p> <p>12 classifications relating to the carcino --</p> <p>13 carcinogenicity of different agents?</p> <p>14 A I am.</p> <p>15 Q The next document in your folder that also</p> <p>16 has some underlining and highlighting is on "Talc</p> <p>17 Translocation from the Vagina to the Oviducts and</p> <p>18 Beyond."</p> <p>19 (Exhibit 9 was marked for identification</p> <p>20 and is attached to the transcript.)</p> <p>21 Q (BY MR. ZELLERS) This is an article that</p> <p>22 was published in 1985. The first named author is</p> <p>23 A.P. Wehner.</p> <p>24 Is this also a document that you brought</p> <p>25 here today?</p>
<p style="text-align: right;">Page 35</p> <p>1 the underlining in this document?</p> <p>2 A Yes, I did.</p> <p>3 Q We'll mark that document, your copy, as</p> <p>4 Exhibit 5.</p> <p>5 (Exhibit 5 was marked for identification</p> <p>6 and is attached to the transcript.)</p> <p>7 Q (BY MR. ZELLERS) I see here that there is</p> <p>8 the IARC monograph dated 2010 on the evaluation of</p> <p>9 carcinogenic risk to humans.</p> <p>10 The bottom part of page 1 is torn off. Do</p> <p>11 you know why that is?</p> <p>12 A I do not.</p> <p>13 Q All right. So the first page gives a date</p> <p>14 reference of 2010. The second page gives -- well,</p> <p>15 it also lists a 2006 date and a 2010 date. There is</p> <p>16 highlighting throughout.</p> <p>17 Whose highlighting is contained in the</p> <p>18 document that we'll mark as Exhibit 6?</p> <p>19 A That would be mine.</p> <p>20 (Exhibit 6 was marked for identification</p> <p>21 and is attached to the transcript.)</p> <p>22 Q (BY MR. ZELLERS) We then have a news</p> <p>23 article from the British Medical Journal that was</p> <p>24 published December 28 of 2008. It's just a one-page</p> <p>25 document with underlining and writing on it.</p>	<p style="text-align: right;">Page 37</p> <p>1 A It is.</p> <p>2 Q The highlighting in the document, is that</p> <p>3 your document -- strike that.</p> <p>4 Is that your highlighting?</p> <p>5 A It -- it is.</p> <p>6 Q Are all of these documents either on your</p> <p>7 reference list or on your Materials Considered List,</p> <p>8 other than what you told us about at the start of</p> <p>9 the deposition?</p> <p>10 A Yes.</p> <p>11 Q We have Deposition Exhibit 47 from the</p> <p>12 Pier deposition. I will not mark that.</p> <p>13 We have an article here by Shukla,</p> <p>14 S H U K L A, "Alterations in Gene Expression in</p> <p>15 Human Mesothelial Cells Correlate with Mineral</p> <p>16 Pathogenicity."</p> <p>17 (Exhibit 10 was marked for identification</p> <p>18 and is attached to the transcript.)</p> <p>19 Q (BY MR. ZELLERS) Is that a document that</p> <p>20 you brought here today?</p> <p>21 A Yes, it is.</p> <p>22 Q Are the highlights and writing on that</p> <p>23 document yours?</p> <p>24 A Yes, they are.</p> <p>25 Q You have an article by Biz'Zard that was</p>



<p style="text-align: right;">Page 38</p> <p>1 published in -- is that -- Phytotherapy Research,  2 2007; is that right?  3 A Yes.  4 Q There do not appear to be any handwriting  5 on that document, so I won't mark it.  6 We have got the Hopkins Deposition  7 Exhibit 28. There's no highlighting on that  8 document.  9 And then we have the "Draft Screening  10 Assessment" from Health Canada dated December 2018.  11 Is the highlighting in that document  12 yours?  13 A Yes, it is.  14 Q All right. We'll mark that as  15 Deposition Exhibit 11.  16 (Exhibit 11 was marked for identification  17 and is attached to the transcript.)  18 Q (BY MR. ZELLERS) Have we covered all of  19 the documents that you have brought with you today  20 in your blue folder?  21 A Yes.  22 Q All right. Let me see your two notebooks  23 that you also have brought with you today. One  24 notebook is "Talc Articles I." The second notebook  25 is "Talc Articles II."</p>	<p style="text-align: right;">Page 40</p> <p>1 Q Did you have any staff that helped you in  2 terms of your review of materials and preparation of  3 your report other -- other than Dr. Hall?  4 A I had a copy editor -- once I had a draft  5 of my report -- review it.  6 Q Who is your copy editor?  7 A Her name is Chris Tachibana.  8 Q And where is she employed?  9 A She is a freelance medical copy editor.  10 Q What role did she play in your review and  11 analysis of materials and your -- the preparation of  12 your report?  13 A So she played no role in the review -- or  14 the drafting of the report, but she reviewed a draft  15 near the end for grammatical issues to remove  16 redundancy.  17 She's someone I work with a great deal for  18 my medical publications, and so --  19 Q You have worked with her in the past -- I  20 --  21 A That's right --  22 Q -- is that right?  23 A -- yes.  24 Q Is she here in the San Francisco area?  25 A She is not.</p>
<p style="text-align: right;">Page 39</p> <p>1 Are all of the articles that are contained  2 in these two notebooks, articles that are contained  3 either on your reference list or on your reliance  4 materials list?  5 A Yes, they are.  6 Q As I go through this quickly, it appears  7 that there is underlining and highlighting of the  8 articles that you have brought here today; is that  9 right?  10 A Yes, it is.  11 Q Is all of the highlighting and underlining  12 and marking, are those your highlights and marking?  13 A Yes, they are.  14 Q Who prepared the notebooks? And let's  15 mark Talc Articles I, the entire notebook as  16 Exhibit 12.  17 (Exhibit 12 was marked for identification  18 and is attached to the transcript.)  19 Q (BY MR. ZELLERS) Talc Articles II, the  20 entire notebook, as Exhibit 13.  21 (Exhibit 13 was marked for identification  22 and is attached to the transcript.)  23 Q (BY MR. ZELLERS) Who prepared Exhibits 12  24 and 13 for you?  25 A I did.</p>	<p style="text-align: right;">Page 41</p> <p>1 Q Where is she located?  2 A She splits her time between Seattle,  3 Washington, and Germany.  4 Q She charges for her services; is that  5 right?  6 A She does.  7 Q Are those charges that you paid or that  8 were paid by plaintiffs' counsel?  9 A They have not yet been paid, but the plan  10 is for her to submit those invoices. And it will  11 come out of my fees, but will be paid by the  12 counsel.  13 Q All right. When you submit invoices,  14 will -- the charges for the copy editor, will those  15 be included in your invoice to plaintiffs' counsel?  16 A My plan is for it to come out of my fee.  17 So I am paying for it, but it should be literally  18 paid by counsel, since I'm not able to pay and  19 deduct taxes or pay taxes or -- or so -- or...  20 Q All right. You will pay it out of your  21 pocket and will not include it on your statement to  22 plaintiffs' counsel; is that right?  23 A That's correct.  24 Q Approximately how much have you paid or  25 will you pay to your copy editor?</p>

<p style="text-align: right;">Page 42</p> <p>1 A I believe the total is in the ballpark of                  2 about 1,500 or \$1,700.                  3 Q How about Dr. Hall? Are her fees being                  4 paid by you or are they being paid by plaintiffs'                  5 counsel?                  6 A Her fees are being paid by counsel.                  7 Q Dr. Hall either has or will submit her own                  8 separate invoice relating to her work on this                  9 matter?                  10 A Yes.                  11 Q Has she already done that?                  12 A I believe she has submitted it. I -- I'm                  13 not 100 percent sure.                  14 Q Do you know what Dr. Hall's fees are at                  15 least through the present time relating to her work                  16 on this matter?                  17 A I believe the amount is in the ballpark of                  18 the same 1,500 to \$2,000.                  19 Q You believe, though, that Dr. Hall either                  20 has or will be submitting invoice -- an invoice                  21 separately for her work to plaintiffs' counsel; is                  22 that right?                  23 A Yes.                  24 Q You have submitted invoices; is that                  25 right?</p>	<p style="text-align: right;">Page 44</p> <p>1 Q What did that lawyer tell you or ask you                  2 about this engagement?                  3 A They told me that there was a -- a case                  4 that they would like some epidemiology research on                  5 and that they thought I would be a very good fit and                  6 would I be willing to speak with them.                  7 I don't believe they even told me what the                  8 content of -- of the case was about, but rather,                  9 that it was a case. And the role that they were                  10 seeking was as an epidemiologist, not as a                  11 radiologist or on the medical care.                  12 Q Was this a phone call or an e-mail or how                  13 did they contact you?                  14 A I believe it was a short e-mail followed                  15 by a short phone call.                  16 Q I mean, do you keep those e-mails? And if                  17 at some point we ask for them to be produced, is                  18 that something you could do?                  19 A For the particular e-mail that you are                  20 asking about, I cannot find it. So I don't have                  21 that. I looked.                  22 Q You were contacted by a lawyer or law                  23 firm, asked if you would be willing.                  24 You said you would be willing without even                  25 knowing what the matter related to?</p>
<p style="text-align: right;">Page 43</p> <p>1 A I have.                  2 Q When were you first retained in this                  3 matter -- well, strike that.                  4 When were you first contacted with                  5 respect to this litigation, the talcum powder MDL?                  6 A My recollection is mid-2017.                  7 Q Who contacted you in mid-2017?                  8 A I was initially contacted by a law firm                  9 that i believe was helping the law firms find expert                  10 witnesses and asked if I would be willing to speak                  11 with them to see if this could be something that I                  12 would be interested in doing.                  13 Q What law firm or lawyer contacted you                  14 initially in mid-2017?                  15 A I -- I don't remember that initial                  16 contact.                  17 Q You don't remember the name of the lawyer                  18 or the law firm that initially contacted you in this                  19 matter?                  20 A The initial law firm basically asked me if                  21 I would be willing to speak to these lawyers, and I                  22 do not know the name of that lawyer who originally                  23 contacted me.                  24 Q Did you ever speak to that lawyer again?                  25 A No.</p>	<p style="text-align: right;">Page 45</p> <p>1 A I didn't say I would be willing to be an                  2 expert. I said I would be willing to have a                  3 conversation with the lawyers to learn about the                  4 case.                  5 Q Were you told at that time that the case                  6 related to talcum powder?                  7 A I was not.                  8 Q Were you told at that time that the                  9 medical issue in the case related to ovarian cancer?                  10 A I do not believe I was.                  11 Q What is the next contact then that you had                  12 with any lawyer relating to this matter?                  13 A So then a phone call was set up between                  14 myself and, I believe it was, three lawyers involved                  15 in this litigation and told about the -- what the --                  16 what the case was about and told what they were                  17 looking for to see if I would be interested in                  18 speaking with them.                  19 And that lead to an in-person meeting                  20 where we then discussed what the case was about.                  21 Q When was the phone call with the three                  22 attorneys?                  23 A All of this was in mid-2017, June-July                  24 time frame.                  25 Q The same question. When was the in-person</p>



<p style="text-align: right;">Page 46</p> <p>1 meeting?</p> <p>2 A Within that same -- maybe a month later,</p> <p>3 but same time frame.</p> <p>4 Q Was the in-person -- strike that.</p> <p>5 Where was the in-person meeting?</p> <p>6 A It was in my office in San Francisco.</p> <p>7 Q Who were the three attorneys that you</p> <p>8 spoke with initially over the phone and then met</p> <p>9 with in person?</p> <p>10 A So Dr. Thompson was one; John Restaino was</p> <p>11 one; and a third lawyer whose name is alluding me.</p> <p>12 Q Was it a man or a woman?</p> <p>13 A A woman.</p> <p>14 Q Is it a lawyer that you have had any</p> <p>15 further contact with or communications with?</p> <p>16 A Yes.</p> <p>17 Q But you can't remember her name?</p> <p>18 A I can't. But if we give it a minute, I</p> <p>19 think I will be able to.</p> <p>20 Q Well, if you do remember it at some point</p> <p>21 today, let us know.</p> <p>22 When you had the phone call with</p> <p>23 Ms. Thompson and with Mr. Restaino and this third</p> <p>24 lawyer in the in-person meeting, what did they ask</p> <p>25 you to do?</p>	<p style="text-align: right;">Page 48</p> <p>1 Q (BY MR. ZELLERS) You understood they</p> <p>2 represented the Plaintiffs in this litigation --</p> <p>3 A Yes.</p> <p>4 Q -- is that right?</p> <p>5 A Yes.</p> <p>6 Q You told them that you would be willing to</p> <p>7 do the review. You did not at that point agree to</p> <p>8 serve as an expert witness for the Plaintiffs; is</p> <p>9 that fair?</p> <p>10 A That's fair.</p> <p>11 Q Did you then go and do your review,</p> <p>12 literature review?</p> <p>13 A Yes, I did.</p> <p>14 Q You, at least at that point in time, had</p> <p>15 never previously done any research or review</p> <p>16 relating to talcum powder or relating to any</p> <p>17 potential association between talcum powder,</p> <p>18 perineal talcum powder use, and ovarian concern; is</p> <p>19 that right?</p> <p>20 A That's correct.</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 Q (BY MR. ZELLERS) You went out and reviewed</p> <p>23 the literature; is that right?</p> <p>24 A Yes.</p> <p>25 Q Did plaintiff's counsel, the two lawyers</p>
<p style="text-align: right;">Page 47</p> <p>1 A They asked me if I would be willing to do</p> <p>2 a comprehensive and unbiased review of the</p> <p>3 literature around talcum powder products and ovarian</p> <p>4 cancer.</p> <p>5 Q Did they ask you to do anything else?</p> <p>6 A Well, they asked if I would be willing to</p> <p>7 be an expert witness in this case.</p> <p>8 Q Anything else?</p> <p>9 A Nothing else that I can recall.</p> <p>10 Q You said you would do a review of the</p> <p>11 literature, correct?</p> <p>12 A I -- yes --</p> <p>13 Q You --</p> <p>14 A -- I did.</p> <p>15 Q -- you said that you would be willing to</p> <p>16 serve as an expert for Plaintiffs, correct?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A I -- I hesitated on the last question</p> <p>19 because I was very upfront and clear that I was</p> <p>20 willing to do a review, but that I did not know this</p> <p>21 field in any great depth and that I would only be</p> <p>22 interested in doing that if I was permitted to do</p> <p>23 the review the same as I do in my other scientific</p> <p>24 work and that I didn't know if my conclusion would</p> <p>25 support my becoming an expert on their behalf.</p>	<p style="text-align: right;">Page 49</p> <p>1 that you met -- well, strike that.</p> <p>2 The three lawyers you met with, did they</p> <p>3 provide you with some articles to get started with?</p> <p>4 A They provided access to a database, a</p> <p>5 Dropbox, where they had a large number of articles</p> <p>6 that they made available to me.</p> <p>7 Q You reviewed those articles. Did you then</p> <p>8 have another meeting or communication with the</p> <p>9 plaintiffs' lawyers?</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A I had several meetings with the lawyers</p> <p>12 over the subsequent year.</p> <p>13 Q (BY MR. ZELLERS) Eventually were you</p> <p>14 asked, you know, to render an opinion on a topic or</p> <p>15 topics?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A I -- I was asked to draft a report of my</p> <p>18 review of the -- the literature and the data that</p> <p>19 were available.</p> <p>20 Q (BY MR. ZELLERS) At this time were there</p> <p>21 any new lawyers that you were meeting with on the</p> <p>22 plaintiffs' side or was it still the three original</p> <p>23 lawyers?</p> <p>24 A They were -- I -- I believe those would</p> <p>25 be -- I think there was one additional lawyer</p>

<p style="text-align: right;">Page 50</p> <p>1 that --</p> <p>2 Q Do you remember his or her name?</p> <p>3 A Her name. Breanne was her first name.</p> <p>4 Q Do you know Breanne's last name?</p> <p>5 A Maybe Cope or something that's similar to</p> <p>6 Cope.</p> <p>7 Q You reviewed the articles. You were asked</p> <p>8 then by Plaintiffs to write up something relating to</p> <p>9 the articles; is that right?</p> <p>10 A Yes.</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 Q (BY MR. ZELLERS) At some point did either</p> <p>13 you suggest or the plaintiff lawyers ask you to form</p> <p>14 certain opinions relating to this matter?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A I'm not -- I'm not sure what you mean,</p> <p>17 "form opinions."</p> <p>18 Q (BY MR. ZELLERS) You met with the lawyers;</p> <p>19 is that right, after you had done your literature</p> <p>20 review?</p> <p>21 A Yes.</p> <p>22 Q You had not yet agreed to be an expert</p> <p>23 witness for the Plaintiffs; is that right?</p> <p>24 A Yes.</p> <p>25 Q After you had done your literature review,</p>	<p style="text-align: right;">Page 52</p> <p>1 better than what you have already done?</p> <p>2 A No.</p> <p>3 Q As part of serving as an expert for</p> <p>4 Plaintiffs, you did an -- either A -- do you call it</p> <p>5 a systematic review or a meta-analysis? What do you</p> <p>6 call that?</p> <p>7 A I call it a systematic review.</p> <p>8 Q What's the difference between a systematic</p> <p>9 review and a meta-analysis?</p> <p>10 A I -- I don't think there's any difference.</p> <p>11 They're -- they're both trying to describe an</p> <p>12 unbiased, quantitative review of the medical</p> <p>13 literature.</p> <p>14 Q Did -- your systematic review that you</p> <p>15 did, you did that after you had done this review of</p> <p>16 the literature, fair?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A My systematic review grew out of my</p> <p>19 reading the literature and realizing that there was</p> <p>20 a real gap, which I thought needed to be filled.</p> <p>21 And I chose to do that.</p> <p>22 Q (BY MR. ZELLERS) I will today, you know,</p> <p>23 ask you some more detailed questions about that.</p> <p>24 Let me make sure I have covered by basics here.</p> <p>25 Your report includes as attachments, a</p>
<p style="text-align: right;">Page 51</p> <p>1 did the plaintiffs' lawyer say: Well,</p> <p>2 Dr. Smith-Bindman, do you have an opinion as to</p> <p>3 whether or not there's an association between</p> <p>4 perineal talcum powder use and ovarian cancer?</p> <p>5 A I don't remember any such conversation.</p> <p>6 I -- I think from the very beginning the lawyers</p> <p>7 were guessing that I was going to feel strongly that</p> <p>8 there's a strong association. So I don't remember</p> <p>9 being retained as an expert after my report came</p> <p>10 out.</p> <p>11 At -- at some point I think it became</p> <p>12 clear to them when I explained my views that they</p> <p>13 would like to have me be an expert.</p> <p>14 But I don't remember a particular</p> <p>15 conversation where they asked me to -- where they</p> <p>16 linked my being an expert to the finished product of</p> <p>17 the report. By the time I drafted the report, they</p> <p>18 knew that they had wanted me to be an expert in this</p> <p>19 case.</p> <p>20 Q All right. At -- at some point after you</p> <p>21 had reviewed the literature and you sat and you</p> <p>22 talked with plaintiffs' counsel, you became an</p> <p>23 expert witness for the Plaintiffs; is that right?</p> <p>24 A Yes.</p> <p>25 Q Are you able to time that for us any</p>	<p style="text-align: right;">Page 53</p> <p>1 list of references; is that right?</p> <p>2 A Yes, it does.</p> <p>3 Q What is meant to be included in the</p> <p>4 references that appear and are attached to your</p> <p>5 report, pages 42 through 47?</p> <p>6 A Those are references that I have cited</p> <p>7 specifically in my report.</p> <p>8 Q In addition along with your report, you</p> <p>9 provided a curriculum vitae; is that right?</p> <p>10 A Yes.</p> <p>11 Q We'll mark that as Exhibit 14.</p> <p>12 (Exhibit 14 was marked for identification</p> <p>13 and is attached to the transcript.)</p> <p>14 MS. O'DELL: Thank you.</p> <p>15 Q (BY MR. ZELLERS) The curriculum vitae that</p> <p>16 is attached as -- strike that -- that you provided</p> <p>17 with your report and that we have marked as</p> <p>18 Exhibit 14, is that complete and up to date?</p> <p>19 A Yes, it is.</p> <p>20 Q Any additions or corrections that need to</p> <p>21 be made to that?</p> <p>22 A There are some details of recent</p> <p>23 publications that are not provided in this, but</p> <p>24 those are relatively minor changes.</p> <p>25 Q Are any of -- the details to publications</p>

<p style="text-align: right;">Page 54</p> <p>1 that you would update your curriculum vitae to, do                  2 any of those relate to this matter or to the                  3 opinions you're giving here today?                  4 A They do not.                  5 Q Deposition Exhibit 15 is also a document                  6 that was provided along with your report. It                  7 appears to be a reliance list; is that right?                  8 MS. O'DELL: Object to the form. Thank                  9 you.                  10 (Exhibit 15 was marked for identification                  11 and is attached to the transcript.)                  12 A Yes, it is.                  13 Q (BY MR. ZELLERS) What is included on the                  14 reliance list which we have marked as a Exhibit 14?                  15 A This is a broad list of --                  16 THE COURT REPORTER: 15.                  17 Q (BY MR. ZELLERS) Oh, I'm sorry. Yes let                  18 me ask that question again.                  19 What documents are listed and included on                  20 the reliance list which we have marked as                  21 Exhibit 15?                  22 A That is a broader list of documents. It                  23 includes documents that I may have read, but I                  24 didn't believe needed to be cited.                  25 It also includes documents that counsel</p>	<p style="text-align: right;">Page 56</p> <p>1 the report in that manner, but just to clarify.                  2 A No, I could not easily go through and pick                  3 out which ones were ones that I provided to them or                  4 which ones they provided to me.                  5 Q (BY MR. ZELLERS) All right. Are you aware                  6 -- do you know who Dr. Judith Wolf is?                  7 A No, I do not. I know the name, but not                  8 the person.                  9 Q Are you aware that your reliance list or                  10 additional Materials Considered List, what we have                  11 marked as Exhibit 15, is identical to the Materials                  12 Considered List that was attached to Dr. Wolf's                  13 report?                  14 A I -- I don't know who Dr. Wolf is, nor do                  15 I know her reliance list.                  16 Q All right. Exhibit 15 is a reliance list                  17 or Materials Considered List that was prepared by                  18 counsel for Plaintiffs; is that right?                  19 A It was the list provided to me.                  20 Q You may have reviewed some of these                  21 documents -- or you have reviewed some of these                  22 documents, but potentially not all of these                  23 documents --                  24 MS. O'DELL: Object to the form.                  25 Q (BY MR. ZELLERS) -- fair?</p>
<p style="text-align: right;">Page 55</p> <p>1 provided to me that -- that may or may not have been                  2 closely read.                  3 So it includes both articles I know very                  4 many, as well as additional documents I may not have                  5 as deep of a knowledge of.                  6 Q Was -- Deposition Exhibit 15, was that                  7 prepared by you or was that prepared by counsel?                  8 A That was prepared by counsel.                  9 Q Have you reviewed all of the references                  10 and materials that are listed out on Deposition                  11 Exhibit 15?                  12 A I -- I do not know. I would have to go                  13 through them one at a time to know if I had reviewed                  14 all of them.                  15 Q Can you easily tell us which of the                  16 materials listed on Exhibit 15, your reliance list,                  17 were provided by you and which were provided by                  18 counsel?                  19 MS. O'DELL: Objection. Objection to                  20 form. I think the documents and materials                  21 considered -- materials and data considered list.                  22 MR. ZELLERS: Well, there's no caption at                  23 the top. I have tried to be as descriptive as I can                  24 with the witness on it.                  25 MS. O'DELL: I think it's referred to in</p>	<p style="text-align: right;">Page 57</p> <p>1 A Yes.                  2 Q Looking at your report, Deposition                  3 Exhibit 2 -- and let me withdraw that.                  4 Have we covered now all of the documents                  5 that you have either reviewed and relied upon in                  6 preparing your opinions in this matter and your                  7 report, which we marked as Exhibit 2, or that were                  8 made available to you and you may or may not have                  9 looked at them?                  10 MS. O'DELL: Object to the form.                  11 A Yes.                  12 Q (BY MR. ZELLERS) Is your report,                  13 Exhibit 2, accurate?                  14 A Yes, it is.                  15 Q Is your report, Exhibit 2, complete, other                  16 than perhaps citing to some of the documents that                  17 you reviewed after preparing your report that we                  18 identified earlier today?                  19 A Yes, it is.                  20 Q There were -- withdraw that.                  21 You have a fee schedule. You're charging                  22 a thousand dollars an hour to review materials and                  23 talk with the lawyers in this matter and provide                  24 opinions; is that right?                  25 A Yes.</p>

<p style="text-align: right;">Page 58</p> <p>1 Q I kind of got sidetracked in terms of 2 asking you about the Plaintiff lawyers that you met 3 with. 4 We had gotten up to your meeting with 5 Ms. Thompson, with Mr. Restaino, with a lawyer 6 perhaps with the first name of Breanne; is that 7 correct? 8 A Yep. 9 Q Have you remembered the fourth lawyer yet? 10 A I -- I have not. Can -- can I call a 11 friend? 12 Q No. No, need to call a friend. 13 What other Plaintiff lawyers have you met 14 with relating to your work as a plaintiff expert for 15 the MDL litigation? 16 A There are no others that I recall. 17 Q We have other lawyers here today. You met 18 them -- 19 A I apologize. 20 Q -- at least in the last day or two? 21 A Yes. 22 Q Well, don't apologize to me. You probably 23 hurt their feelings. 24 Did you meet all of the lawyers who are 25 here today at some point?</p>	<p style="text-align: right;">Page 60</p> <p>1 most of the day yesterday, did you have any other 2 meetings or conversations with the lawyers for the 3 Plaintiffs to prepare for your deposition? 4 A Yes, I did. So today is Thursday. 5 Wednesday, we met for most of the day. And I met 6 with Dr. Thompson for an hour or so on Wednesday as 7 well. 8 Q All right. Any other -- 9 MS. O'DELL: I think the days may be mixed 10 up. You said "Wednesday" twice. 11 A I apologize. So Tuesday, we met at the 12 end of the day for an hour and then most of the day 13 yesterday, Wednesday, and then today. Thank you. 14 Q (BY MR. ZELLERS) Any other meetings or 15 communications with counsel for Plaintiffs to 16 prepare for the deposition here today? 17 A Any other in-person meetings or -- 18 Q Or phone calls in which there was, you 19 know, discussion about preparing for the deposition. 20 A I believe over -- well, I had asked to 21 reschedule this deposition. So there were a couple 22 of e-mails related to that. 23 I also had asked for a couple of 24 additional documents to help ensure that I was 25 seeing all materials that I felt were relevant to</p>
<p style="text-align: right;">Page 59</p> <p>1 A Yes, I did. 2 Q Some of them you have met just in the last 3 couple of days as you prepared for the deposition; 4 is that right? 5 A That's correct. 6 Q Other than the lawyers who are present in 7 the room today for Plaintiffs, have you met with any 8 other lawyers or communicated with any other lawyers 9 that you believe represent the Plaintiffs in this 10 litigation? 11 A I have not. 12 Q What did you do to prepare for your 13 deposition here today? 14 A My primary preparation was to review my 15 report and to reaccess references that I included in 16 my report to make sure that I was aware of the 17 details or -- or relevant... 18 Q What else did you do to prepare for your 19 deposition here today? 20 A I also met with the lawyers yesterday to 21 review the process of the deposition and so forth. 22 Q How long did you meet with the lawyers 23 yesterday? 24 A We met most of the day yesterday. 25 Q Other than meeting with the lawyers for</p>	<p style="text-align: right;">Page 61</p> <p>1 the case. 2 Q Are those the materials that were on 3 Exhibit 3 that we talked about at the very 4 beginning? 5 A Yes, they are. 6 Q Anything else that you did with the 7 lawyers in terms of preparing for your deposition 8 here today? 9 A No. 10 MS. O'DELL: Dr. Smith-Bindman, feel free 11 to testify regarding meetings, when they happened, 12 phone calls, et cetera, but not the substance of 13 those discussions. 14 A Okay. 15 MS. O'DELL: Thank you. 16 Q (BY MR. ZELLERS) Any others? 17 A None that I can remember. 18 Q Ms. Thompson -- did you know Ms. Thompson 19 before she initially called you and then came and 20 sat down to meet with you? 21 A Initially, you -- 22 Q Yes. 23 A -- mean? No, I did not. 24 Q Had you ever worked with Ms. Thompson on 25 any other litigation?</p>

<p style="text-align: right;">Page 62</p> <p>1 A No.</p> <p>2 Q Other than the talcum powder litigation</p> <p>3 that we're here deposing you in, have you worked on</p> <p>4 other litigations for either defendants or</p> <p>5 plaintiffs?</p> <p>6 MS. O'DELL: Other than the ones she has</p> <p>7 testified to?</p> <p>8 Q (BY MR. ZELLERS) Well, other than, yes,</p> <p>9 the cases.</p> <p>10 A No, I have not.</p> <p>11 Q You have served as an expert witness in</p> <p>12 other matters in which you did not provide</p> <p>13 deposition testimony; is that right?</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A There are a small number of additional</p> <p>16 medical malpractice cases that I was also involved</p> <p>17 with which would have settled before I was asked to</p> <p>18 take a deposition.</p> <p>19 Q (BY MR. ZELLERS) My question is: Have you</p> <p>20 ever testified or consulted with either plaintiffs</p> <p>21 or defense in -- in a product liability litigation</p> <p>22 like this?</p> <p>23 A I have not.</p> <p>24 Q Have you ever provided testimony in a</p> <p>25 matter relating to a consumer product?</p>	<p style="text-align: right;">Page 64</p> <p>1 Q Do the invoices go through the time that</p> <p>2 you prepared your opinions and report as of</p> <p>3 November 15 of 2018?</p> <p>4 A Yes, they will.</p> <p>5 Q All right. Is that where they end?</p> <p>6 A They would also include some hours that I</p> <p>7 have worked reviewing the material since that time.</p> <p>8 Although, I don't believe I have submitted those</p> <p>9 reports -- those invoices, but I certainly can.</p> <p>10 Q So my question is: How much time have you</p> <p>11 spent on this matter since your last invoice? Can</p> <p>12 you estimate that for us?</p> <p>13 A I would guess in the ballpark of 10 hours,</p> <p>14 not including the time I met with the lawyers</p> <p>15 yesterday -- not this week. Excluding the time this</p> <p>16 week.</p> <p>17 Q How much time did you spend this week in</p> <p>18 addition to that 10 hours with the lawyers in</p> <p>19 preparing yourself to provide deposition testimony?</p> <p>20 A In the ballpark of another 10 hours.</p> <p>21 Q Have you been served or been asked to</p> <p>22 serve as an expert witness or consultant in any</p> <p>23 other talcum powder litigation or matters?</p> <p>24 A I have not.</p> <p>25 Q What percent of your professional time do</p>
<p style="text-align: right;">Page 63</p> <p>1 A I have not.</p> <p>2 Q Have you ever been retained as an expert</p> <p>3 or provided testimony in a matter relating to</p> <p>4 asbestos?</p> <p>5 A I have not.</p> <p>6 Q Mr. Restaino -- had you ever met</p> <p>7 Mr. Restaino before that initial phone call and</p> <p>8 meeting back in mid-2017?</p> <p>9 A I had not.</p> <p>10 Q When I look at your invoices, will they</p> <p>11 generally outline the times that you had meetings</p> <p>12 and communications with Plaintiff lawyers?</p> <p>13 A Yes, they will.</p> <p>14 Q Will they also outline whatever work</p> <p>15 that -- and I don't mean work, but at least dates as</p> <p>16 to when you began your systematic review or</p> <p>17 meta-analysis?</p> <p>18 A The work that I did will be itemized. I'm</p> <p>19 not sure if I break down writing the report versus</p> <p>20 doing the systematic review into separate buckets,</p> <p>21 but it might.</p> <p>22 Q The invoices will start with sometime in</p> <p>23 mid-2017, when you started meeting with the lawyers;</p> <p>24 is that right?</p> <p>25 A Yes.</p>	<p style="text-align: right;">Page 65</p> <p>1 you spend working as a consultant?</p> <p>2 A A small amount. Probably less than</p> <p>3 5 percent.</p> <p>4 Q What percent of your income is from</p> <p>5 consulting on litigation matters?</p> <p>6 MS. O'DELL: For a particular year or time</p> <p>7 period or average, just --</p> <p>8 Q (BY MR. ZELLERS) Well, the last couple of</p> <p>9 years.</p> <p>10 A In the last couple of years, a -- a small</p> <p>11 amount. Probably 5 or 10 percent.</p> <p>12 Q What is the largest percent of your income</p> <p>13 that has related to consulting on litigation</p> <p>14 matters?</p> <p>15 And what I'm asking you to do is to look</p> <p>16 back. And what was the high point in terms of</p> <p>17 income that you received from consulting on</p> <p>18 medical/legal matters?</p> <p>19 A Probably the 10 percent that I cited.</p> <p>20 Q Have you ever attended a convention or a</p> <p>21 meeting with plaintiff lawyers and other plaintiff</p> <p>22 experts?</p> <p>23 A I have not.</p> <p>24 Q Never?</p> <p>25 A A meeting of lawyers?</p>



<p style="text-align: right;">Page 66</p> <p>1 Q Yes, a meeting of lawyers --</p> <p>2 A Never.</p> <p>3 Q -- and plaintiff experts.</p> <p>4 A Never.</p> <p>5 Q All right. Have you --</p> <p>6 A I didn't know there was such a thing.</p> <p>7 Q Do you know any of the experts that have</p> <p>8 also been retained by the Plaintiffs in this</p> <p>9 litigation?</p> <p>10 A I don't know them personally, but I -- I</p> <p>11 have seen their names. And their names are the</p> <p>12 same -- some of the names are names that are</p> <p>13 familiar to me.</p> <p>14 Q Have you communicated with any of the</p> <p>15 other experts for Plaintiffs?</p> <p>16 A I have not.</p> <p>17 Q Have you reviewed reports from any of the</p> <p>18 experts for Plaintiffs?</p> <p>19 A I have reviewed a handful of them --</p> <p>20 Q What --</p> <p>21 A -- yes.</p> <p>22 Q -- reports of other plaintiff experts have</p> <p>23 you reviewed?</p> <p>24 A I reviewed Dr. Cooke's report. I reviewed</p> <p>25 Mr. Longo's report. I reviewed an ob --</p>	<p style="text-align: right;">Page 68</p> <p>1 Q What others?</p> <p>2 A Mr. Cooke's deposition, I believe.</p> <p>3 Q What others? Did you put in your report,</p> <p>4 the names of other experts that you reviewed their</p> <p>5 deposition testimony of?</p> <p>6 A I -- I -- I'm checking if -- if I have.</p> <p>7 I...</p> <p>8 Q Well, you have a recollection of reviewing</p> <p>9 --</p> <p>10 A -- I -- I don't have a recollection of any</p> <p>11 others that I have looked at.</p> <p>12 Q Do you know who David Kessler is?</p> <p>13 A I do.</p> <p>14 Q How do you know Dr. Kessler?</p> <p>15 A I --</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A -- Dr. Kessler is a faculty member at</p> <p>18 UCSF.</p> <p>19 Q (BY MR. ZELLERS) Do you know him</p> <p>20 personally?</p> <p>21 A Not well, but enough to say hello.</p> <p>22 Q Been at meetings with him?</p> <p>23 A I have.</p> <p>24 Q You understand that he's an expert for the</p> <p>25 Plaintiffs?</p>
<p style="text-align: right;">Page 67</p> <p>1 obstetrician gynecologist report.</p> <p>2 Q Do you remember who?</p> <p>3 A Clarke perhaps or something like Clarke.</p> <p>4 MS. O'DELL: If you need to refer to your</p> <p>5 report or your materials, feel free to do that.</p> <p>6 A Okay. I think Mr. Cralley's (phonetic)</p> <p>7 report.</p> <p>8 Q (BY MR. ZELLERS) Do you know any of those</p> <p>9 experts personally?</p> <p>10 A I do not.</p> <p>11 Q All right. You have never communicated</p> <p>12 with any of those experts; is that right?</p> <p>13 A I have not.</p> <p>14 Q You have just reviewed their reports; is</p> <p>15 that right?</p> <p>16 A That's correct.</p> <p>17 Q Have you reviewed any deposition testimony</p> <p>18 or portions of depositions of plaintiff experts in</p> <p>19 this matter?</p> <p>20 A I have reviewed small pieces of several of</p> <p>21 them.</p> <p>22 Q Okay. What experts have you reviewed a --</p> <p>23 small pieces of their deposition?</p> <p>24 A Dr. Moorman's testimony or deposition, I</p> <p>25 saw some of.</p>	<p style="text-align: right;">Page 69</p> <p>1 A I -- I have been told that.</p> <p>2 Q Have you had any discussions with</p> <p>3 Dr. Kessler at all relating to this matter, the</p> <p>4 talcum powder matter?</p> <p>5 A I have not.</p> <p>6 Q Have you participated in any projects --</p> <p>7 medical/legal projects with Dr. Kessler --</p> <p>8 A I --</p> <p>9 Q -- in the past?</p> <p>10 A -- I have not.</p> <p>11 Q Have you heard of a documentary called</p> <p>12 "The Bleeding Edge"?</p> <p>13 A I have.</p> <p>14 Q Did you participate in the documentary</p> <p>15 called "The Bleeding Edge"?</p> <p>16 A I did.</p> <p>17 Q You understand that Dr. Kessler also</p> <p>18 participated in that; is that right?</p> <p>19 A I -- yes.</p> <p>20 Q That is a documentary related to what?</p> <p>21 A A medical devices, primarily.</p> <p>22 Q Have you served as a consultant or expert</p> <p>23 in medical device matters?</p> <p>24 A I have not.</p> <p>25 Q Pharmaceutical matters?</p>



<p style="text-align: right;">Page 70</p> <p>1 A I have not.</p> <p>2 Q How was it then that you were retained or</p> <p>3 ended up participating in "The Bleeding Edge"</p> <p>4 documentary?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A I -- I'm not sure if you have had a chance</p> <p>7 to see the documentary or not, but my role in it</p> <p>8 is -- is pretty off topic.</p> <p>9 And so at an initial incarnation of that</p> <p>10 documentary, they had thought about focusing on an</p> <p>11 issue where I do do research, radiation for medical</p> <p>12 imaging.</p> <p>13 It no longer fits into their new topic,</p> <p>14 but somehow they kept a quote of me in that film.</p> <p>15 Q Did -- Dr. Kessler, was he the one</p> <p>16 responsible for putting that documentary together?</p> <p>17 A I -- no, I don't -- I don't believe he</p> <p>18 was.</p> <p>19 Q Were you paid for your work in</p> <p>20 participating in that documentary?</p> <p>21 A No I was not.</p> <p>22 Q All right. Jane Hall, she assisted you</p> <p>23 with your systematic review. Is -- is that the</p> <p>24 right way you would characterize it, a systematic</p> <p>25 review?</p>	<p style="text-align: right;">Page 72</p> <p>1 A I had --</p> <p>2 Q -- in this case --</p> <p>3 A -- not.</p> <p>4 Q -- is that right?</p> <p>5 A That's correct.</p> <p>6 Q Have you worked with other</p> <p>7 biostatisticians in the past?</p> <p>8 A I have.</p> <p>9 Q Why did you decide you needed to work with</p> <p>10 a new biostatistician for this litigation?</p> <p>11 A The primary work that I needed was to do a</p> <p>12 few graphs and figures, and so I wanted someone who</p> <p>13 was both an expert in that and who I thought could</p> <p>14 respond relatively quickly.</p> <p>15 I have on my team, several</p> <p>16 biostatisticians who are part of my research group,</p> <p>17 but they don't have particularly relevant expertise</p> <p>18 in generating these graphs.</p> <p>19 And it would have required them to acquire</p> <p>20 some skills, and so I wanted someone who focuses</p> <p>21 specifically on this who could do that.</p> <p>22 Q Did you review any work from Dr. Hall</p> <p>23 before you hired her?</p> <p>24 A I have been involved in systematic reviews</p> <p>25 that she contributed to that I was very impressed</p>
<p style="text-align: right;">Page 71</p> <p>1 A Yes, the systematic review -- you asked</p> <p>2 the difference between a meta-analysis. It sort of</p> <p>3 implies a certain scientific review -- rigor when</p> <p>4 you call it a systematic review, so that's how I</p> <p>5 like to think about it.</p> <p>6 Q You think systematic review implies more</p> <p>7 scientific rigor than meta-analysis?</p> <p>8 A I think it's a subtle distinction, but</p> <p>9 yes, I do.</p> <p>10 Q Well, you communicated and hired Jane hall</p> <p>11 to assist you; is that right?</p> <p>12 A Yes, I did.</p> <p>13 Q Have you produced all of your</p> <p>14 communications and materials with Jane Hall?</p> <p>15 A I have.</p> <p>16 Q How did you come in contact with Dr. Hall?</p> <p>17 A I work closely with an emergency medicine</p> <p>18 researcher, and I have assisted him in several</p> <p>19 systematic reviews.</p> <p>20 And I knew he had a biostatistician who</p> <p>21 generated the kind of graphics and analysis that I</p> <p>22 wanted. And so I reached out to him, and he</p> <p>23 introduced me to Dr. Hall.</p> <p>24 Q You had never worked with Dr. Hall prior</p> <p>25 to performing your systematic review --</p>	<p style="text-align: right;">Page 73</p> <p>1 with. And so --</p> <p>2 Q So what other --</p> <p>3 A -- I reached out.</p> <p>4 Q -- sorry. I didn't mean to interrupt you.</p> <p>5 What other systematic reviews have you</p> <p>6 been involved with Dr. Hall?</p> <p>7 A Actually, two of them. One of them is on</p> <p>8 a treatment for kidney stones. Ralph Wang is the</p> <p>9 senior author.</p> <p>10 And the second was a systematic review</p> <p>11 around the diagnosis of and treatment for pulmonary</p> <p>12 embolism that also Dr. Wang was the leader on.</p> <p>13 Q Did you ever meet with Dr. Hall with</p> <p>14 respect to this work in person?</p> <p>15 A I never met with her related to anything.</p> <p>16 It was all by electronic communication.</p> <p>17 Q Did you ever talk with her over the phone?</p> <p>18 A Yes. We spoke a few times.</p> <p>19 Q Did you take notes of your conversations</p> <p>20 with Dr. Hall?</p> <p>21 A Not that I recall.</p> <p>22 Q You did have e-mails with Dr. Hall --</p> <p>23 A Yes.</p> <p>24 Q -- is that right?</p> <p>25 A Yes.</p>

<p style="text-align: right;">Page 74</p> <p>1 Q Do you have receipts for the work that 2 Dr. Hall performed for you? 3 MS. O'DELL: Object to the form. 4 A Like an invoice receipt? 5 Q (BY MR. ZELLERS) Yes, an invoice receipt. 6 A No, I do not. 7 Q You ended up paying her rush fees so that 8 she would do the work and the analysis more quickly; 9 is that right? 10 MS. O'DELL: Object to the form. 11 A I -- I remember telling her I didn't mind 12 her rush fee. But -- but all of the invoicing was 13 done directly with counsel. 14 Q (BY MR. ZELLERS) Well, Dr. Hall came to 15 you and said: You know, it's going to take X amount 16 of time to do a thorough analysis? 17 A Yes. 18 Q She did offer to rush the analysis -- 19 A Yes. 20 Q -- when you told her you needed it? 21 A Yes. 22 Q And your recollection is she, you know, 23 did rush the analysis and -- and got it done within 24 a couple of days? 25 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 76</p> <p>1 time is 11:10 a.m. 2 Q (BY MR. ZELLERS) Dr. Smith-Bindman, I'm 3 handing you Deposition Exhibit 16, which is an 4 e-mail chain. The very first e-mail, meaning the 5 last e-mail at the top of page 1, is Jane Hall -- 6 from Jane Hall, September 24, 2018, at 8:04 a.m. to 7 you. 8 (Exhibit 16 was marked for identification 9 and is attached to the transcript.) 10 Q (BY MR. ZELLERS) Will you take a look at 11 that and tell us if that is a printout of some of 12 your e-mail exchanges with Dr. Hall? 13 A Yes. 14 Q If we go to the very first e-mail in the 15 chain, it appears that you contacted Dr. Hall on 16 Wednesday, September 19, 2018, in the afternoon, 17 3:21 p.m., and told her that you were interested 18 primarily in generating a forest plot with a summary 19 estimate and test for heterogeneity; is that right? 20 A Yes. 21 Q That was your initial contact with 22 Dr. Hall; is that right? 23 A Yes. 24 Q You contacted your referring person, 25 Ralph, on the e-mail; is that right?</p>
<p style="text-align: right;">Page 75</p> <p>1 A I believe the analysis actually took a 2 couple of weeks. 3 But I was very open to paying her rush 4 fee. I thought her fee was extraordinarily 5 reasonable, and so it just made it easier for me to 6 get it done quickly rather than to delay. 7 Q (BY MR. ZELLERS) You defer to the e-mails 8 and the documents as to the timing of when you 9 requested that she rush the analysis and when she 10 provided it to you; is that right? 11 MS. O'DELL: Object to the form. 12 A I believe my documents would be correct 13 about when I asked for stuff and when it was done, 14 yes. 15 MS. O'DELL: Excuse me, Mike. We have 16 been going about an hour and 20 minutes. Is this a 17 good time to take a quick break? 18 MR. ZELLERS: Absolutely. 19 THE VIDEOGRAPHER: We are off the record. 20 The time is 10:40 a.m. This is the end of Disc 1. 21 (A break was taken from 10:40 a.m. to 22 11:10 a.m.) 23 THE VIDEOGRAPHER: We are back on the 24 record. This marks the beginning of Disc No. 2 in 25 the deposition of Dr. Rebecca Smith-Bindman. The</p>	<p style="text-align: right;">Page 77</p> <p>1 A Yes. 2 Q All right. You told -- the next day you 3 had some exchanges of e-mails with Dr. Hall. You 4 told Dr. Hall that because you were doing a review 5 for a legal case, you did not need the detail that 6 you would need for a paper; is that right? 7 MS. O'DELL: Object to the form. 8 A Can you tell me where you're reading? 9 Q (BY MR. ZELLERS) Sure. I'm reading on 10 page 2 of Exhibit 16, the very last e-mail. This is 11 from you on September 20 of 2018. 12 You thanked Dr. Hall for her willingness 13 to help. 14 "As Ralph mentioned, I am doing a review 15 for a legal case and don't need quite the detail I 16 would usually need for a paper." 17 Is that what you told Dr. Hall? 18 A Yes, it is. 19 Q As of -- well, you communicated with 20 Dr. Hall on Friday, September 21st, in the 21 morning. This is the very last e-mail on page 1 of 22 Exhibit 16. 23 You asked her to send you whatever she was 24 doing sooner rather than later because you needed to 25 get your report finished ASAP; is that right?</p>

<p style="text-align: right;">Page 78</p> <p>1 MS. O'DELL: Object to the form. I think 2 you misstated date on the e-mail but -- 3 Q (BY MR. ZELLERS) Well, I'm sorry. Let me 4 ask that question again. On Friday morning, 5 September 21, 2018, you told Dr. Hall that you 6 needed her information as soon as possible because 7 you had to finish your report ASAP; is that right? 8 A Yes. 9 Q Dr. Hall got back to you that day and 10 said, you know, I'll do my best. But if you want, I 11 can rush the work, if you're willing to pay time and 12 a half. 13 You then got back to her on Monday 14 morning, September 24, and said: Yes, I'll pay the 15 rush fee, and I would like your work as soon as 16 possible. 17 Is that right? 18 MS. O'DELL: Object to the form. Object 19 to the form. 20 A I -- I think you're paraphrasing what it 21 says. The -- the idea was she said that if I paid 22 the rush, she could have some money to defray 23 childcare cost during -- 24 Q (BY MR. ZELLERS) Right. And -- 25 A -- that time, and I agreed to do that.</p>	<p style="text-align: right;">Page 80</p> <p>1 A Yes. 2 Q Have you communicated about this 3 litigation with anyone other than the plaintiffs' 4 counsel that you have told us about with Dr. Hall? 5 Anyone else? 6 MS. O'DELL: Object to the form. 7 A I -- you asked me if I have mentioned this 8 litigation to anyone else? 9 Q (BY MR. ZELLERS) Well, let's start there. 10 Have you mentioned this litigation to anyone else? 11 A I have. 12 Q Who have you mentioned this litigation to? 13 A I have certainly mentioned it to my 14 husband. 15 Q Other than your husband? 16 A And then I have mentioned it to several 17 close friends. 18 Q Your husband is a physician; is that 19 right? 20 A He is. 21 Q Did he provide any professional input to 22 you related to your review of this matter? 23 A No, he did not. 24 Q The close friends that you mentioned this 25 to, did they provide any input or assistance or</p>
<p style="text-align: right;">Page 79</p> <p>1 Q Exactly. And she said back to you: Okay. 2 By the end of -- so this is on a Monday. She said 3 you'll have the work product from her Wednesday at 4 the earliest, probably Thursday. 5 "I should have at least two sets of plots 6 today, and I'll send them to you as they are 7 output." 8 Is that right? 9 A Yes. 10 Q You have produced all of your e-mails and 11 communications with Dr. Hall in this matter; is that 12 right? 13 A I have. You're not showing me all of 14 those communications; is that right? 15 Q I haven't yet. 16 A Okay. 17 Q I'm going to show you some more. 18 A Yes. 19 Q But my question to you is: Included in 20 the production, at least you have included all of 21 your communications -- 22 A Yes. 23 Q -- with Dr. Hall -- 24 A Yes. 25 Q -- is that right?</p>	<p style="text-align: right;">Page 81</p> <p>1 direction to you relating to this matter? 2 A No. 3 Q I asked you before if you read any of the 4 depositions of the plaintiff experts. Have you 5 discussed generally with plaintiffs' counsel, the 6 deposition testimony that's been given by other 7 plaintiff experts in this litigation? 8 MS. O'DELL: I would instruct you not to 9 answer that question. 10 MR. ZELLERS: I disagree, but we'll 11 reserve that issue. 12 Q (BY MR. ZELLERS) Was there anything that 13 you asked plaintiffs' counsel to provide to you in 14 connection with your review or for preparation of 15 your report that you were not provided with? 16 A So most of the documents that I included 17 in my report, I found by doing an independent search 18 online. 19 There were several items that I didn't 20 find that I wanted to review as well. And so some 21 of the items that I asked counsel for were items 22 that I couldn't find through scientific research 23 that I asked them to provide. 24 Q And you have told us about those 25 documents, and those are listed out on Exhibit 3; is</p>

<p style="text-align: right;">Page 82</p> <p>1 that right?</p> <p>2 A That's correct.</p> <p>3 Q My question was a little bit different.</p> <p>4 Is there anything that you asked for from</p> <p>5 plaintiffs' counsel that they were not able or did</p> <p>6 not provide to you?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A I -- I can't think of anything that fits</p> <p>9 into that question.</p> <p>10 Q (BY MR. ZELLERS) Take a look at your</p> <p>11 reliance list, which we have marked as Deposition</p> <p>12 Exhibit 15.</p> <p>13 Do you have that in front of you?</p> <p>14 A I have my copy of the reliance list. I</p> <p>15 don't have your Exhibit 15 in front of me.</p> <p>16 Q If you have your copy -- does it start</p> <p>17 with page 1?</p> <p>18 A Yes, it does.</p> <p>19 Q At the very top --</p> <p>20 A Yes.</p> <p>21 Q -- the first item is "A Survey of The</p> <p>22 Long-Term Effects"?</p> <p>23 A Yes.</p> <p>24 Q If you turn to pages 11 and 12, there's a</p> <p>25 series of documents that begin with "IMERYS"</p>	<p style="text-align: right;">Page 84</p> <p>1 MR. ZELLERS: Sure. Exhibit 3 is the list</p> <p>2 you gave me today of -- of the documents that</p> <p>3 Dr. Smith-Bindman reviewed in addition to whatever</p> <p>4 else is marked.</p> <p>5 MS. O'DELL: -- I see. I see.</p> <p>6 MR. ZELLERS: So there's a -- it's a list</p> <p>7 of Bates-stamped documents.</p> <p>8 MS. O'DELL: Yes.</p> <p>9 MR. ZELLERS: There's 10 or 12 Imerys</p> <p>10 documents. There's one J&amp;J Bates-stamped document</p> <p>11 --</p> <p>12 MS. O'DELL: Right.</p> <p>13 MR. ZELLERS: -- and then there's the, I</p> <p>14 think, expert report or --</p> <p>15 MS. O'DELL: Right.</p> <p>16 MR. ZELLERS: -- deposition of Dr. Cooke</p> <p>17 listed?</p> <p>18 MS. O'DELL: Right. Okay. I just object</p> <p>19 to the form of the question. And -- and --</p> <p>20 A Could I --</p> <p>21 MS. O'DELL: -- then --</p> <p>22 A -- see Exhibit 3?</p> <p>23 MS. O'DELL: -- yes. And then I would --</p> <p>24 Counsel, permit me -- there was a question related</p> <p>25 to Exhibit 3. I thought you were referring to the</p>
<p style="text-align: right;">Page 83</p> <p>1 followed by numbers.</p> <p>2 Do you see that?</p> <p>3 A I do.</p> <p>4 Q Do you know whether or not you reviewed</p> <p>5 some or all of those Imerys-produced documents as</p> <p>6 part of your review in this matter?</p> <p>7 A If those reflect Imerys testing documents</p> <p>8 then yes, I did review at least some of them. I</p> <p>9 can't be sure all of them.</p> <p>10 Q Do you know whether or not these documents</p> <p>11 relate to Imerys testing?</p> <p>12 A I have reviewed at least a half dozen</p> <p>13 Imerys testing documents.</p> <p>14 Q In --</p> <p>15 A I believe that's what these are, but I --</p> <p>16 I'm not sure.</p> <p>17 Q There are a number of Imerys documents</p> <p>18 that are listed on Exhibit 3, which you identified</p> <p>19 as testing documents; is that right?</p> <p>20 A Yes.</p> <p>21 Q Do you know if you reviewed any Imerys</p> <p>22 documents other than the documents that are listed</p> <p>23 out on Exhibit 3?</p> <p>24 MS. O'DELL: Can you just make a --</p> <p>25 Exhibit 3, would you remind --</p>	<p style="text-align: right;">Page 85</p> <p>1 materials list, and so I'm going to assert my</p> <p>2 objection a little bit late.</p> <p>3 MR. ZELLERS: Okay. I just want to move</p> <p>4 forward.</p> <p>5 MS. O'DELL: I know that you do.</p> <p>6 MR. ZELLERS: Yes.</p> <p>7 MS. O'DELL: I just want to be clear.</p> <p>8 Because Exhibit 3 that we provided were additional</p> <p>9 materials that Dr. Smith-Bindman asked for and</p> <p>10 reviewed in addition to the Materials Considered. I</p> <p>11 don't want the record to be unclear. So --</p> <p>12 MR. ZELLERS: Well --</p> <p>13 MS. O'DELL: -- I have noted my objection.</p> <p>14 MR. ZELLERS: -- and the record is clear</p> <p>15 that Dr. Smith-Bindman did not review all of the</p> <p>16 materials listed in the Materials Considered List,</p> <p>17 Exhibit 15. But that testimony will stand as it is.</p> <p>18 My question just is: In addition to the</p> <p>19 documents that I was told about this morning that</p> <p>20 you believe are testing documents, do you know</p> <p>21 whether you reviewed any other Imerys-produced</p> <p>22 documents, and specifically the ones that are</p> <p>23 itemized on pages 11 and 12 of your Materials</p> <p>24 Considered List?</p> <p>25 A I would need to see those documents to</p>

<p style="text-align: right;">Page 86</p> <p>1 know if I reviewed them. The names are awfully  2 nonspecific.</p> <p>3 Q With respect to the Imerys documents -- or  4 Imerys-produced documents that are identified in  5 Exhibit 15, which is your Materials Considered List,  6 do you know how those were compiled?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A You're asking me where this list came  9 from?</p> <p>10 Q (BY MR. ZELLERS) I think you have told us  11 the list came from plaintiffs' counsel; is that  12 right?</p> <p>13 A Yes.</p> <p>14 Q My question then, I guess, is more  15 precise. Do you know how plaintiffs' counsel  16 compiled this list of Imerys-produced documents or  17 how they selected those documents?</p> <p>18 A I know I had a lot of back and forth in  19 generating this list with actually Breanne at the  20 time. I sent her a lot of documents that I had  21 looked at that I hadn't cited that she added to the  22 list.</p> <p>23 These were ones that she added to the  24 list, and I don't remember what they were.</p> <p>25 Q I'm going to ask my question again. Do</p>	<p style="text-align: right;">Page 88</p> <p>1 litigation -- so when you do your research work or  2 when you do your publishing work -- do you rely on  3 documents that are picked by someone else that may  4 not represent the full body of evidence?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A In my work, I review whatever data are  7 available. And sometimes those data are identified  8 by me and sometimes they have been given to me by  9 other sources to review.</p> <p>10 Q (BY MR. ZELLERS) Is that a -- a yes or a  11 no? And let me withdraw that.</p> <p>12 The documents that we have looked at in  13 your reliance list Materials Considered List that  14 begin with Imerys and begin with J&amp;J, your  15 understanding, those are documents that have been  16 produced by the Defendants in this litigation; is  17 that right?</p> <p>18 A Yes.</p> <p>19 Q Do you know what percentage of the overall  20 documents that have been produced by Johnson &amp;  21 Johnson companies and by Imerys, these documents  22 that are listed in Exhibit 15, represent?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A Are you asking me if the handful of  25 documents from Johnson &amp; Johnson that are in this</p>
<p style="text-align: right;">Page 87</p> <p>1 you know how -- these documents, the documents that  2 are on pages 11 and 12 of your Materials Considered  3 List that begin with the "Imerys" name, do you know  4 how they were compiled?</p> <p>5 A No.</p> <p>6 Q All right. The same question. If you  7 look on page 13 of your Materials Considered List,  8 there's a series of documents that have J&amp;J and then  9 a number; is that right?</p> <p>10 A Yes.</p> <p>11 Q You, as we sit here, do not know what  12 those documents relate to; is that right?</p> <p>13 A That's correct.</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 Q (BY MR. ZELLERS) You do not know how this  16 listing of J&amp;J documents was compiled; is that  17 right?</p> <p>18 A That's correct.</p> <p>19 Q These are documents produced by Imerys and  20 by Johnson &amp; Johnson companies as part of this  21 overall list of materials that were available, you  22 know, for you to review; is that right?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A Yes.</p> <p>25 Q (BY MR. ZELLERS) Outside of your work in</p>	<p style="text-align: right;">Page 89</p> <p>1 list reflect all of the documents ever created at  2 Johnson &amp; Johnson or all relevant documents or --</p> <p>3 Q (BY MR. ZELLERS) Do you have any idea?</p> <p>4 A No, no idea.</p> <p>5 Q This is a handful of documents that have  6 been listed out by plaintiffs' counsel for you; is  7 that right?</p> <p>8 A Yes.</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A Yes.</p> <p>11 Q (BY MR. ZELLERS) All right. In your  12 report you cite two exhibits from the depositions of  13 several witnesses. There's an exhibit from a  14 deposition of John Hopkins.</p> <p>15 Do you know who John Hopkins is?</p> <p>16 A I know what the document is, but I -- I  17 don't know what -- who John Hopkins is.</p> <p>18 Q Do you know what company he works for?</p> <p>19 A I do not.</p> <p>20 Q Do you know what his position or title is?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 Q (BY MR. ZELLERS) You're looking in your  23 materials at the exhibit that you were provided from  24 his deposition; is that right?</p> <p>25 A Yes. I -- I -- I do not --</p>



<p style="text-align: right;">Page 90</p> <p>1 Q Have --</p> <p>2 A -- see.</p> <p>3 Q -- you read any portion of the deposition</p> <p>4 of John Hopkins?</p> <p>5 A I have not.</p> <p>6 Q Have you reviewed any other exhibits from</p> <p>7 the deposition of John Hopkins?</p> <p>8 A I have not.</p> <p>9 Q Do you know who Julie Pier is?</p> <p>10 A I believe I do.</p> <p>11 Q Who is Julie Pier?</p> <p>12 A I -- I'm just checking. I -- I -- I got a</p> <p>13 few names wrong earlier, so I want to just check</p> <p>14 if --</p> <p>15 Q Well, you're going back now and you are</p> <p>16 looking at your report?</p> <p>17 A Yes.</p> <p>18 Q And you have annotated your report, I</p> <p>19 guess, that you are using here today; is that right?</p> <p>20 A Yes.</p> <p>21 Q Why don't we -- just so we have a complete</p> <p>22 record, we'll mark your annotated report as</p> <p>23 Exhibit 17.</p> <p>24 A Yes.</p> <p>25 (Exhibit 17 was marked for identification</p>	<p style="text-align: right;">Page 92</p> <p>1 Q All right. You were provided -- just as</p> <p>2 you were for the exhibit from the deposition of John</p> <p>3 Hopkins, you were provided with the exhibit that you</p> <p>4 are reviewing from Julie Pier's deposition; is that</p> <p>5 right?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A No, I don't -- well, I -- I don't believe</p> <p>8 that's why I know who she is.</p> <p>9 I -- I believe The New York Times story</p> <p>10 and the Reuters story discussed her deposition. So</p> <p>11 I don't remember reading her deposition. But I --</p> <p>12 if I'm not confusing her with someone else, I think</p> <p>13 that's where I learned about her testing.</p> <p>14 Q (BY MR. ZELLERS) Okay. You're a couple of</p> <p>15 questions ahead of me here. No. 1, the exhibit</p> <p>16 that's in your blue folder from the deposition of</p> <p>17 Julie Pier, that was provided to you for review by</p> <p>18 counsel for Plaintiffs; is that right?</p> <p>19 A Thank you for that reminder. That's the</p> <p>20 Imerys document. Yes. Yes.</p> <p>21 Q I'm going to go back to my question.</p> <p>22 A Yes.</p> <p>23 Q The exhibit from Julie Pier's deposition,</p> <p>24 that was provided to you for review by plaintiffs'</p> <p>25 counsel; is that right?</p>
<p style="text-align: right;">Page 91</p> <p>1 and is attached to the transcript.)</p> <p>2 A And -- and I would like to clarify based</p> <p>3 on some of my notes. But -- so I think Dr. Hopkins</p> <p>4 oversaw testing for -- for talc products at J&amp;J.</p> <p>5 Q (BY MR. ZELLERS) Is that a note that you</p> <p>6 have on your report?</p> <p>7 A It is.</p> <p>8 Q All right. That's a note that you put on</p> <p>9 your report in preparation for your deposition</p> <p>10 today?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A It's a note I put on my report when I was</p> <p>13 reviewing my report and the documents I'm citing and</p> <p>14 so forth.</p> <p>15 Q (BY MR. ZELLERS) Who is Julie Pier? Do</p> <p>16 you know who she is?</p> <p>17 A I'm -- what I believe -- although, I don't</p> <p>18 see that I made a note of it -- is that she was</p> <p>19 someone who did testing from one of the New York</p> <p>20 hospitals of -- of the talc powder products.</p> <p>21 Q Do you know anything more than that about</p> <p>22 Julie Pier or who she worked for or what her role</p> <p>23 with respect to talcum powder was?</p> <p>24 A Now that I am remembering where I -- I --</p> <p>25 no, I don't really know those things.</p>	<p style="text-align: right;">Page 93</p> <p>1 A Yes.</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 Q (BY MR. ZELLERS) You have not reviewed the</p> <p>4 deposition transcript of Ms. Pier; is that right?</p> <p>5 A Not that I recall.</p> <p>6 Q You have not reviewed any exhibit -- other</p> <p>7 exhibits to her deposition; is that right?</p> <p>8 A That is correct.</p> <p>9 Q Are you aware that the two exhibits that</p> <p>10 you were provided by counsel for Plaintiffs -- one</p> <p>11 from the deposition of John Hopkins and one from the</p> <p>12 deposition of Julie Pier -- that those exhibits were</p> <p>13 prepared by plaintiffs' experts for this litigation?</p> <p>14 MS. O'DELL: Object to the form. I think</p> <p>15 you referred to plaintiffs' experts. I think you</p> <p>16 misspoke. You said they were prepared by</p> <p>17 plaintiffs' experts.</p> <p>18 MR. ZELLERS: Well -- and I will ask it</p> <p>19 again then.</p> <p>20 Q (BY MR. ZELLERS) Are you aware that the</p> <p>21 exhibits that were provided to you -- one from</p> <p>22 Ms. Pier's deposition and one from the Hopkins</p> <p>23 deposition -- are exhibits that were prepared by</p> <p>24 Plaintiffs in this litigation?</p> <p>25 MS. O'DELL: Object to the form.</p>



<p style="text-align: right;">Page 94</p> <p>1 A I was provided these documents from a 2 prior case. I don't know who prepared them or where 3 they came from. I -- they were provided to me by 4 counsel. 5 Q (BY MR. ZELLERS) Let me ask you just a 6 couple of background questions from your review of 7 the literature in this case. You have reviewed a 8 lot of literature relating to talcum powder and 9 talcum powder use by women in the perineal region; 10 is that right? 11 A Yes, I have. 12 Q I think you say in your report that you 13 reviewed upwards of 40 studies in papers relating to 14 that. Does that sound about right? 15 MS. O'DELL: Object to the form. 16 A Upward of 40 studies that provided primary 17 new data. There were probably hundreds of papers I 18 reviewed on the topic. 19 Q (BY MR. ZELLERS) From that review, do you 20 agree that most women who use talcum powder in their 21 perineal region begin that use before age 30? 22 A I don't know the -- when -- I -- I think a 23 lot of women start use when they're young. I would 24 have to check my report if I have cites as to when 25 they began using talcum powder products.</p>	<p style="text-align: right;">Page 96</p> <p>1 Q And if we looked at the data for when and 2 the age that women were when they first used genital 3 powder, at least from this study by Dr. Cramer, it 4 appears that the vast majority of women began using 5 talcum powder in their genital area before age 30; 6 is that right? 7 A In this publication. 8 Q Do you recall any other publications 9 that -- that you reviewed that provided contrary 10 information? 11 A The question you're asking me is not one 12 that I spent a lot of time thinking about and so 13 can't recall -- sort of across the hundreds of 14 papers I read and 50 that talked about the 15 association -- what time the age of first use was. 16 I -- I see Dr. Cramer's experience is that 17 women do report beginning use earlier, but I -- 18 there's no way for me to know if that's a reflection 19 of his sampling, the place he studied the women, and 20 so forth. 21 Q At least on that point, you would refer to 22 Dr. Cramer, fair? 23 MS. O'DELL: Object to the form. 24 A I -- I would defer to a comprehensive 25 review of the literature to come up with that view.</p>
<p style="text-align: right;">Page 95</p> <p>1 Q (BY MR. ZELLERS) Well, take a look, if you 2 will, at Deposition Exhibit 18, which is a report by 3 Cramer. 4 (Exhibit 18 was marked for identification 5 and is attached to the transcript.) 6 Q (BY MR. ZELLERS) He's the first named 7 author. This is the 2016 study -- 8 MS. O'DELL: Thank you. 9 Q (BY MR. ZELLERS) -- report. Are you -- 10 MS. O'DELL: Are we at 18? 11 MR. ZELLERS: 18. 12 Q (BY MR. ZELLERS) You're familiar with the 13 paper we have marked as Deposition Exhibit 18; is 14 that right? 15 A Yes, I am. 16 Q I do want to ask you questions a later 17 about that. But for purposes of this question when 18 do most women who use talcum powder -- powder in 19 their perineal region begin, go to page 336 of 20 Exhibit 18 and specifically Table 1. 21 A Yes. 22 Q One of the categories that is reported 23 here in Table 1 is "Age First Used Genital Powder"; 24 is that right? 25 A Yes.</p>	<p style="text-align: right;">Page 97</p> <p>1 My -- my guess would be that Dr. Cramer 2 believes his numbers in his population, but I -- but 3 I don't know that that's the truth in other 4 populations. 5 Q (BY MR. ZELLERS) Well, let me ask you 6 another question. On average from the studies that 7 you reviewed, do women who use talcum powder in 8 their perineal region continue that use for over 9 20 years? 10 MS. O'DELL: Object to the form. 11 A My recollection of the literature is that 12 most publications could not assess or did not ask in 13 detailed enough form of how long women used it. 14 I -- I -- again, it's possibly a question 15 that could be answered from the literature, but I 16 don't recall knowing that answer from my review of 17 the literature. 18 Q (BY MR. ZELLERS) Did you review the Wu 19 2015 paper? 20 A I did. 21 Q Do you have that in one of your notebooks? 22 A I will have it in here. 23 Q That makes it easy. 24 A 2009 or -- 25 Q '15. No. The 2015 Wu paper.</p>

<p style="text-align: right;">Page 98</p> <p>1 A Yes, I do.</p> <p>2 Q Turn to page 1097, Table 2.</p> <p>3 A Could you -- unfortunately, the page --</p> <p>4 the version I have is a free download, and it</p> <p>5 doesn't have the same page --</p> <p>6 Q How --</p> <p>7 A -- numbers.</p> <p>8 Q -- about -- can you find Table 2? It's</p> <p>9 the a table that's captioned "Prevalence of Risk</p> <p>10 Factors in Non-Hispanic white, Hispanic, and</p> <p>11 African-American Control."</p> <p>12 A Yes, I have that paper.</p> <p>13 Q All right. So if you look at the</p> <p>14 controls, at the very bottom of that section, it</p> <p>15 gives a mean number of years of talc use among</p> <p>16 users; is that right?</p> <p>17 A Yes.</p> <p>18 Q And whether we're looking at non-Hispanic</p> <p>19 whites, Hispanics, or African-Americans, at least</p> <p>20 the number of years of talc use that's reported is</p> <p>21 greater than 20 years for each of those groups; is</p> <p>22 that right?</p> <p>23 A In --</p> <p>24 MS. O'DELL: Object to the form.</p> <p>25 A -- in Dr. Wu's paper, there is reported</p>	<p style="text-align: right;">Page 100</p> <p>1 A Yes.</p> <p>2 Q (BY MR. ZELLERS) Are you able to tell us</p> <p>3 how far before you prepared your report, November 15</p> <p>4 of 2018, that you formed those conclusions?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A I spent considerable hours during 2018</p> <p>7 reviewing the literature. And over the course of</p> <p>8 that year, my opinions started to solidify when I</p> <p>9 saw the evidence that strongly supported that</p> <p>10 ovarian cancer is caused by talcum powder products.</p> <p>11 I --</p> <p>12 Q (BY MR. ZELLERS) And --</p> <p>13 A -- I -- I believe that my final systematic</p> <p>14 review was for me important to -- to confirm that</p> <p>15 association. And that wasn't done -- that wasn't</p> <p>16 completed until my report was basically -- close to</p> <p>17 when my report had to be drafted.</p> <p>18 Q The systematic review that you did was in</p> <p>19 and around September and October of 2018; is that</p> <p>20 right?</p> <p>21 A I believe the final statistical analysis</p> <p>22 was then, but my -- my systematic review went on for</p> <p>23 many months.</p> <p>24 Q Well, your systematic review, at least</p> <p>25 insofar as Dr. Hall assisted you, was in September</p>
<p style="text-align: right;">Page 99</p> <p>1 that the mean number of years is greater than 20.</p> <p>2 Q (BY MR. ZELLERS) If we look down at the</p> <p>3 group below, the number of cases, the mean number of</p> <p>4 years of talc use among users is greater than</p> <p>5 20 years, also for each of those groups; is that</p> <p>6 right?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A Dr. Wu found that the average number of</p> <p>9 years was greater than 20, yes.</p> <p>10 Q (BY MR. ZELLERS) All right. You have</p> <p>11 never published on, you know, any topic relating to</p> <p>12 talcum powder or any association between talcum</p> <p>13 powder and ovarian cancer; is that right?</p> <p>14 A I have not.</p> <p>15 Q Your opinion is that women exposed to</p> <p>16 perineal talcum powder products on a regular basis</p> <p>17 have about a 50 percent increase in their subsequent</p> <p>18 risk of developing serous invasive cancer; is that</p> <p>19 correct?</p> <p>20 A Yes, that is my opinion.</p> <p>21 Q You also opine in your report that there</p> <p>22 is a causal association between genital talcum</p> <p>23 powder use and ovarian cancer generally; is that</p> <p>24 right?</p> <p>25 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 101</p> <p>1 of 2018; is that right?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A The systematic review that I described in</p> <p>4 my report has a lot of components. So one component</p> <p>5 is to do a complete comprehensive review of -- of</p> <p>6 what's been published.</p> <p>7 And that involved doing the search,</p> <p>8 according -- obtaining all the papers, and then</p> <p>9 reviewing the bibliography of all of those papers.</p> <p>10 Then reviewing all those papers critically</p> <p>11 and then abstracting data for those papers. Kind of</p> <p>12 towards the tail end of that review is to</p> <p>13 statistically combine the studies.</p> <p>14 Dr. Hall was involved both in abstracting</p> <p>15 the data as a second set of eyes and in doing the</p> <p>16 statistical summary. But I reached out to her after</p> <p>17 all of those initial points were completed. So that</p> <p>18 went on for many months.</p> <p>19 Q (BY MR. ZELLERS) Is it the objective of a</p> <p>20 systematic review to bring clarity to a research</p> <p>21 question by combining like-with-like data?</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 A The purpose of the systematic review is to</p> <p>24 take individual papers that may not have enough</p> <p>25 statistical power to provide by themselves,</p>

<p style="text-align: right;">Page 102</p> <p>1 individual results that are meaningful. And if the</p> <p>2 methodology is combinable, to pool the sample size</p> <p>3 to get greater statistical power to come up with a</p> <p>4 conclusion.</p> <p>5 But your question about combining like</p> <p>6 with like is -- is -- is very important.</p> <p>7 Q (BY MR. ZELLERS) In order for research to</p> <p>8 be useful, it must be valid, correct?</p> <p>9 A Yes.</p> <p>10 Q Inaccurate and incomplete reporting of</p> <p>11 methods can make research unreasonable and unusable;</p> <p>12 is that right?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A I -- I -- I think there are separate</p> <p>15 phases of research that need happen. I think the</p> <p>16 reporting of methodology is so that other people can</p> <p>17 duplicate your results, understand your results.</p> <p>18 But in and of themselves, the reporting</p> <p>19 does not influence the reliability of the -- of the</p> <p>20 research.</p> <p>21 Q (BY MR. ZELLERS) Is reporting of</p> <p>22 methodology important?</p> <p>23 A I -- I think reporting of methodology so</p> <p>24 that other people can duplicate the results is</p> <p>25 important.</p>	<p style="text-align: right;">Page 104</p> <p>1 been done, I tried, in writing my report, to</p> <p>2 highlight the details of what would be needed to</p> <p>3 understand my result.</p> <p>4 But I have not, for example, included</p> <p>5 certain details that you would typically put in a</p> <p>6 journal article.</p> <p>7 So in a journal article, you would always</p> <p>8 publish the version of SAS or R that was used for</p> <p>9 the report. I -- I would not have included that.</p> <p>10 And -- and I believe some of the documents</p> <p>11 I shared with you that Dr. Hall provided to me on</p> <p>12 the methodology were included in the e-mail to me.</p> <p>13 And I may not have included it in the</p> <p>14 report, thinking that the reader would not -- you,</p> <p>15 for example, would be interested in some of those</p> <p>16 biostatistical nuances.</p> <p>17 But when I publish it, I would put those</p> <p>18 in because the readership might care about them.</p> <p>19 Q You talked, I believe, a minute ago about</p> <p>20 abstracting data; is that right?</p> <p>21 A Yes.</p> <p>22 Q Is data abstraction one of the most</p> <p>23 important steps in conducting a meta-analysis or a</p> <p>24 systematic review?</p> <p>25 Would you agree with that?</p>
<p style="text-align: right;">Page 103</p> <p>1 So if -- if I move ahead as I'm planning</p> <p>2 to publish my systematic review, then I would</p> <p>3 include greater details about the methodology so</p> <p>4 that other investigators could duplicate my work,</p> <p>5 should -- should they so choose.</p> <p>6 Q At least as of now, other scientists or</p> <p>7 epidemiologists would not be able to reproduce what</p> <p>8 you have done based upon your report --</p> <p>9 MS. O'DELL: Object --</p> <p>10 Q (BY MR. ZELLERS) -- correct?</p> <p>11 MS. O'DELL: -- object to the form.</p> <p>12 A I am -- I am not sure that that's the</p> <p>13 case.</p> <p>14 Q (BY MR. ZELLERS) Do you think that all of</p> <p>15 the steps that you followed in terms of preparing</p> <p>16 your systematic review are set forth in your report?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A I think the path that I followed in this</p> <p>19 review and the method that I used is a method that I</p> <p>20 have used in a number of other published systematic</p> <p>21 reviews.</p> <p>22 And so to the degree that people could</p> <p>23 sort of say: Well, this is what Dr. Smith-Bindman</p> <p>24 does in a review -- she focuses on stratified</p> <p>25 results -- these are the methods that have done --</p>	<p style="text-align: right;">Page 105</p> <p>1 A I would agree with that.</p> <p>2 Q Would you agree that the accuracy of the</p> <p>3 data abstraction is very important to the validity</p> <p>4 of the analysis?</p> <p>5 A I think one of the hallmarks of doing a</p> <p>6 systematic review is, in fact, to have several</p> <p>7 people abstract the data points so that you can be</p> <p>8 assured that there are -- that they're done as</p> <p>9 accurately as possible, with the understanding of a</p> <p>10 single data abstraction by a single person can never</p> <p>11 be perfect.</p> <p>12 And so the more people that abstract and</p> <p>13 review, the greater the accuracy of the data.</p> <p>14 Q Your data abstraction was not perfect,</p> <p>15 correct?</p> <p>16 A It was not.</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 Q (BY MR. ZELLERS) The data abstraction that</p> <p>19 was done by Dr. Hall was not perfect; is that right?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A That is correct.</p> <p>22 Q (BY MR. ZELLERS) If data is misrepresented</p> <p>23 -- well, strike that.</p> <p>24 Are you familiar with the</p> <p>25 term "misrepresentation"?</p>

<p style="text-align: right;">Page 106</p> <p>1 MS. O'DELL: Object to the form.</p> <p>2 A I -- I will admit I'm not sure what the</p> <p>3 context is you're asking --</p> <p>4 Q (BY MR. ZELLERS) Well --</p> <p>5 A -- about.</p> <p>6 Q -- let me try to put it in another context</p> <p>7 or at least ask a question that may get to what I am</p> <p>8 trying to get to.</p> <p>9 If data is misrepresented from the</p> <p>10 original study, the analysis -- the systematic</p> <p>11 review or the meta-analysis can be comprised,</p> <p>12 correct?</p> <p>13 A Yes, I agree.</p> <p>14 Q Inaccuracy and misrepresentation of data</p> <p>15 are considered violations of generally accepted</p> <p>16 standards of research; is that right?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A Misrepresentation of data suggests to me</p> <p>19 that there's some malicious or devious attempt where</p> <p>20 occasionally there are sometimes simple errors in</p> <p>21 abstraction when you write down the No. 5 and, in</p> <p>22 fact, the number really is .5.</p> <p>23 And often when abstracting data, it's not</p> <p>24 so much an error of writing down 5 or .5, but it's</p> <p>25 choosing which number in that manuscript reflects</p>	<p style="text-align: right;">Page 108</p> <p>1 MS. O'DELL: -- form.</p> <p>2 Q (BY MR. ZELLERS) Go back to my question.</p> <p>3 And -- and with the background that you have given</p> <p>4 and with your qualification, do you agree that</p> <p>5 inaccuracy and misrepresentation are considered</p> <p>6 violations of generally accepted standards of</p> <p>7 research?</p> <p>8 MS. O'DELL: Object to the form. If you</p> <p>9 don't understand the question, you may ask him to</p> <p>10 rephrase it. If --</p> <p>11 A I --</p> <p>12 MS. O'DELL: -- you understand --</p> <p>13 A -- I --</p> <p>14 MS. O'DELL: -- the question, feel free to</p> <p>15 answer it.</p> <p>16 A -- I felt like I had answered the question</p> <p>17 that I understood, so it -- perhaps I'm not</p> <p>18 understanding your question.</p> <p>19 Q (BY MR. ZELLERS) Are you able to answer</p> <p>20 that question?</p> <p>21 A Yes. I think that misrepresentation of</p> <p>22 data is not how I would describe an error in</p> <p>23 abstraction of data or in a difference of opinion</p> <p>24 about what value reflects the data point you were</p> <p>25 looking for. I wouldn't consider that a</p>
<p style="text-align: right;">Page 107</p> <p>1 what you are really trying to capture and get at.</p> <p>2 So typically there are more than one way</p> <p>3 to abstract data. It's why it's not -- it -- it's</p> <p>4 why it's not simply having multiple people so they</p> <p>5 don't make typos or small extraction mistakes, but</p> <p>6 rather, that they're making similar choices.</p> <p>7 And so misrepresentation, the way you have</p> <p>8 asked it, makes it sound like there's some malicious</p> <p>9 attempt to get it wrong or to -- to manipulate it</p> <p>10 rather than the wrong number was chosen for either a</p> <p>11 simple error or because there was a choice and the</p> <p>12 choice was not made in a way that two people would</p> <p>13 agree. And so...</p> <p>14 Q (BY MR. ZELLERS) There can be differences</p> <p>15 in the way different folks go about doing a research</p> <p>16 project or a meta-analysis or a systematic review;</p> <p>17 is that right?</p> <p>18 A Yes.</p> <p>19 Q In order for someone to reproduce or</p> <p>20 replicate what another epidemiologist or scientist</p> <p>21 has done, they need to see the steps that the</p> <p>22 scientist or epidemiologist followed; is that right?</p> <p>23 A That is --</p> <p>24 MS. O'DELL: Object to the --</p> <p>25 A -- correct.</p>	<p style="text-align: right;">Page 109</p> <p>1 misrepresentation of data.</p> <p>2 Q Understood. Let me ask my question once</p> <p>3 more.</p> <p>4 A Okay.</p> <p>5 Q Misrepresentation of data would be a</p> <p>6 violation of generally accepted standards of</p> <p>7 research, correct?</p> <p>8 A I agree that misrepresentation of data</p> <p>9 would be a violation of research.</p> <p>10 Q A causal analysis cannot be determined</p> <p>11 based on a single piece of evidence, but requires</p> <p>12 consideration of the totality of relevant evidence.</p> <p>13 Do you agree with that?</p> <p>14 A I would say in the field of epidemiology,</p> <p>15 it's unusual to have a single piece of evidence.</p> <p>16 But I think in some circumstances a single piece of</p> <p>17 evidence can establish causality. Not typically in</p> <p>18 epidemiology work.</p> <p>19 Q What do you mean in your report by "causal</p> <p>20 association"?</p> <p>21 A So in my report, I did research as -- sort</p> <p>22 of as I outlined in my Table of Contents of, you</p> <p>23 know, number of different areas.</p> <p>24 Q Okay. And I'm going to ask you about</p> <p>25 those. Right now my question just --</p>

<p style="text-align: right;">Page 110</p> <p>1 A No.</p> <p>2 Q -- is --</p> <p>3 A I understand. I --</p> <p>4 Q What --</p> <p>5 A -- understand.</p> <p>6 Q -- do you mean when you say "causal association"?</p> <p>7</p> <p>8 A No. I -- I understand. I -- I apologize.</p> <p>9 I was not getting there quite quickly enough.</p> <p>10 Q That's all right.</p> <p>11 A So I did research on several topics that I</p> <p>12 thought were highly relevant to coming up with a</p> <p>13 causal determination, and I put those different</p> <p>14 pieces of research and expertise together in terms</p> <p>15 of the causality by specifically looking at the</p> <p>16 Bradford Hill criteria.</p> <p>17 Q I -- and I'm going to get to eventually, I</p> <p>18 hope, why you came up with whatever opinion you came</p> <p>19 up with.</p> <p>20 Right now I'm just trying to understand</p> <p>21 what you mean when you use the words "causal</p> <p>22 association."</p> <p>23 MS. O'DELL: Object to the form. Is there</p> <p>24 a specific case in her report that --</p> <p>25 Q (BY MR. ZELLERS) Sure. "Conclusion."</p>	<p style="text-align: right;">Page 112</p> <p>1 Q Is that what you mean by "causal</p> <p>2 association"?</p> <p>3 A Yes, it is.</p> <p>4 Q What are the other causes of ovarian</p> <p>5 cancer?</p> <p>6 A So there's a whole long list of risk</p> <p>7 factors for ovarian cancer.</p> <p>8 Q What is the difference between a risk</p> <p>9 factor and a cause?</p> <p>10 A A risk factor is something that puts you</p> <p>11 at increased risk, increases the probability that</p> <p>12 you will get ovarian cancer. And there are</p> <p>13 innumerable mechanisms and ways that that can go</p> <p>14 about.</p> <p>15 But often -- not entirely, but often, you</p> <p>16 don't think of risk factors as being things that you</p> <p>17 can alter. That's not entirely true.</p> <p>18 There are some risk factors. For example,</p> <p>19 the use of -- well, the -- the most commonly cited</p> <p>20 risk factor for cancer in general is smoking, and</p> <p>21 that's clearly something that can be started or</p> <p>22 ended, that can be changed.</p> <p>23 But often you think of risk factors as</p> <p>24 things that can't be changed. So elevation in age,</p> <p>25 inherited genetics.</p>
<p style="text-align: right;">Page 111</p> <p>1 Page 41 of the report, In conclusion, substantial</p> <p>2 evidence supports a strong, positive, and causal</p> <p>3 association between ovarian cancer and genital</p> <p>4 exposure to talcum powder products.</p> <p>5 I just want to know what you mean when you</p> <p>6 say "causal association."</p> <p>7 MS. O'DELL: I think she answered your</p> <p>8 question.</p> <p>9 But you may answer him, if you understand</p> <p>10 it.</p> <p>11 A I -- I think that the -- the four</p> <p>12 sentences just above that says that, Summary</p> <p>13 consideration of causality of talc powder products</p> <p>14 and ovarian cancer using the Bradford Hill.</p> <p>15 So I -- I -- I believe, using this</p> <p>16 framework, the Bradford Hill, the components of the</p> <p>17 Bradford Hill demonstrate that ovarian cancer is</p> <p>18 caused by regular talcum powder exposure based on</p> <p>19 the strength of the association, based on the</p> <p>20 consistency, the temporality of -- of the components</p> <p>21 of my analysis.</p> <p>22 Q (BY MR. ZELLERS) Do you believe that</p> <p>23 perineal use of talcum powder by women on a regular</p> <p>24 basis causes ovarian cancer?</p> <p>25 A Yes, I do.</p>	<p style="text-align: right;">Page 113</p> <p>1 So those things lead to ovarian cancer,</p> <p>2 the risk factors that I describe in my report. But</p> <p>3 most of them are not things that you can influence.</p> <p>4 Some of them are, but most of them are not.</p> <p>5 Where talcum powder products -- the use of</p> <p>6 perineal talcum powder products -- products is</p> <p>7 something that can be changed. That -- that is a</p> <p>8 behavior, and so I think that's the distinction that</p> <p>9 I would make.</p> <p>10 Q A risk factor is something that increases</p> <p>11 the potential risk of a disease, but cannot be</p> <p>12 changed, correct?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A I -- I said that it's often something that</p> <p>15 can't be changed. But -- but again, there are risk</p> <p>16 factors that, by convention, we consider risk</p> <p>17 factors, but that are modifiable.</p> <p>18 Q (BY MR. ZELLERS) All right.</p> <p>19 A And I gave smoking as an example.</p> <p>20 Q A cause of a disease is something that can</p> <p>21 be modified; is -- is that correct?</p> <p>22 A It --</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A -- again, it is often used that way.</p> <p>25 Q (BY MR. ZELLERS) What makes a factor cross</p>



<p style="text-align: right;">Page 114</p> <p>1 the line from being a risk factor to being a cause?</p> <p>2 A I -- I think what I was suggesting is it's</p> <p>3 a blurry distinction. I think it's by convention</p> <p>4 things that cannot be modified are typically thought</p> <p>5 as risk factors. Things that can be modified are</p> <p>6 generally thought about as being in the causal</p> <p>7 family -- pathway.</p> <p>8 But there's no distinction that you can</p> <p>9 separate something that increases your risk of</p> <p>10 something versus something that causes it. The --</p> <p>11 the causal pathways could be the exact same causal</p> <p>12 pathways in both situations.</p> <p>13 Q What other causes are there of ovarian</p> <p>14 cancer?</p> <p>15 A So I'm guessing from what I have just said</p> <p>16 that you are asking about causes and risk factors or</p> <p>17 would you like them to be --</p> <p>18 Q Well, do you use "risk factor" and "cause"</p> <p>19 interchangeably or are they different?</p> <p>20 MS. O'DELL: Object to the form; asked and</p> <p>21 answered.</p> <p>22 A I -- I believe that by convention we</p> <p>23 typically describe risk factors that are things that</p> <p>24 cannot be altered.</p> <p>25 But technically there is no difference</p>	<p style="text-align: right;">Page 116</p> <p>1 Smoking is a possible risk factor.</p> <p>2 So all of those are in the category of</p> <p>3 risk factors for ovarian cancer.</p> <p>4 Q My question goes to cause. Based upon</p> <p>5 your review of the literature over the past year,</p> <p>6 what other causes of ovarian cancer have you</p> <p>7 identified, if any?</p> <p>8 MS. O'DELL: Objection to form; asked and</p> <p>9 answered.</p> <p>10 A There are other contributors to ovarian</p> <p>11 cancer like pelvic inflammatory disease, which I</p> <p>12 think was on the list of what I just noted.</p> <p>13 There are no other modifiable factors that</p> <p>14 I would put on the list of things that cause ovarian</p> <p>15 cancer other than exposure to talc powder products.</p> <p>16 Q (BY MR. ZELLERS) Based upon your review of</p> <p>17 the literature in terms of a cause for ovarian</p> <p>18 cancer, the only cause that you have identified is</p> <p>19 the regular perineal use of talcum powder by women,</p> <p>20 correct?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 Misstates her testimony.</p> <p>23 A I believe I just said that pelvic</p> <p>24 inflammatory disease increases the risk of ovarian</p> <p>25 cancer.</p>
<p style="text-align: right;">Page 115</p> <p>1 between factors, covariants that influence your</p> <p>2 cancer risk that you can change or not. So I can</p> <p>3 tell you the list of things that fall into those two</p> <p>4 categories.</p> <p>5 Q (BY MR. ZELLERS) All right. What I want</p> <p>6 to know is: Based upon your review and your</p> <p>7 research over the past year or so, other than</p> <p>8 perineal use of talcum powder on a regular basis,</p> <p>9 what other causes of ovarian cancer are there?</p> <p>10 A So in my report on page 11, I write that,</p> <p>11 Numerous risk factors are identified for ovarian</p> <p>12 cancer. Unfortunately, few can be modified by</p> <p>13 therapies or lifestyle changes. Risk factors</p> <p>14 include personal or family history of -- of cancer,</p> <p>15 inherited mutations, BRC1 and BRC2, advanced age,</p> <p>16 white, race, education, endometriosis.</p> <p>17 Other factors that may increase --</p> <p>18 increase ovarian cancer due to estrogen exposure</p> <p>19 include having no pregnancies or advanced age at</p> <p>20 first birth, obesity, post menopausal hormone</p> <p>21 therapy.</p> <p>22 Several factors I list are associated with</p> <p>23 a decreased risk of ovarian cancer such as breast</p> <p>24 feeding or multiple pregnancies, oral</p> <p>25 contraceptions, tubal ligation, or hysterectomy.</p>	<p style="text-align: right;">Page 117</p> <p>1 Q (BY MR. ZELLERS) Is pelvic in --</p> <p>2 MS. O'DELL: Excuse me. I'm sorry. Were</p> <p>3 you finished, Dr. Smith-Bindman? I mean, if you're</p> <p>4 not, you -- you may continue. If so, I apologize --</p> <p>5 A I --</p> <p>6 MS. O'DELL: -- for interrupting you both.</p> <p>7 A -- I was going to add that endometriosis</p> <p>8 has been noted also as a contributor to --</p> <p>9 Q (BY MR. ZELLERS) Is -- are you finished?</p> <p>10 A -- I am.</p> <p>11 Q Okay. Is pelvic inflammatory disease a</p> <p>12 cause of ovarian cancer?</p> <p>13 A I -- I -- you -- you keep asking me the</p> <p>14 same question, and I don't understand the</p> <p>15 distinction that you are asking me to make between</p> <p>16 something that causes cancer and something that's a</p> <p>17 risk factor.</p> <p>18 In both situation -- situations there is a</p> <p>19 probability of getting a disease versus not getting</p> <p>20 a disease. There's no 100 percent association, and</p> <p>21 so most people, as an analogy who smoke cigarettes,</p> <p>22 do not get lung cancer. It's fewer than 15 percent.</p> <p>23 Does smoking cause lung cancer? Yes. Is</p> <p>24 it a risk factor for lung cancer? Yes. Is it a</p> <p>25 single pathway that everyone who smokes, gets lung</p>



<p style="text-align: right;">Page 118</p> <p>1 cancer? No.</p> <p>2 So I -- you're asking me to make a</p> <p>3 distinction that I don't make in my head, so I'm --</p> <p>4 I'm not sure -- all of the things I suggested as</p> <p>5 risk factors in some women will cause them to have</p> <p>6 cancer.</p> <p>7 Q You are opining in this case that the</p> <p>8 regular perineal use of talcum powder causes ovarian</p> <p>9 cancer, correct?</p> <p>10 A Yes, I am.</p> <p>11 Q My question is: Does pelvic inflammatory</p> <p>12 disease cause ovarian cancer?</p> <p>13 A In some women, pelvic inflammatory disease</p> <p>14 will cause cancer.</p> <p>15 Q You -- you would list a pelvic</p> <p>16 inflammatory disease as a cause of ovarian cancer;</p> <p>17 is that your testimony?</p> <p>18 MS. O'DELL: Objection, asked and</p> <p>19 answered.</p> <p>20 A I would include pelvic inflammatory</p> <p>21 disease with all the other ovarian cancer risk</p> <p>22 factors like BRCA1 and 2 as being one of a large</p> <p>23 number of contributors and risk factors for ovarian</p> <p>24 cancer.</p> <p>25 There -- there is not -- no other</p>	<p style="text-align: right;">Page 120</p> <p>1 Q (BY MR. ZELLERS) Have you done anything to</p> <p>2 advise the health community about your belief that</p> <p>3 there is a causal association between talcum powder</p> <p>4 use and ovarian cancer?</p> <p>5 A I have mentioned to you that I have spoken</p> <p>6 about my review to several individuals, several</p> <p>7 close mentors of mine in leadership roles within the</p> <p>8 healthcare community. So I --</p> <p>9 Q Who?</p> <p>10 A -- not -- not individuals I am willing to</p> <p>11 name.</p> <p>12 Q You won't tell me who you have talked to</p> <p>13 about your belief or your theory that there's a</p> <p>14 causal association between genital talcum powder use</p> <p>15 and ovarian cancer?</p> <p>16 A I would prefer not to share that</p> <p>17 information.</p> <p>18 Q Have you contacted any public health</p> <p>19 authorities such as the FDA or the National Cancer</p> <p>20 Institute?</p> <p>21 A I have not.</p> <p>22 Q Have you written any type of an op-ed or</p> <p>23 other news article on this topic?</p> <p>24 A Not yet. I have not.</p> <p>25 Q You have done that in the past; is that</p>
<p style="text-align: right;">Page 119</p> <p>1 exposure -- a modifiable exposure that I can think</p> <p>2 of that leads to getting ovarian cancer or causing</p> <p>3 ovarian cancer.</p> <p>4 Q (BY MR. ZELLERS) In -- in your practice as</p> <p>5 a radiologist, you do not evaluate what caused an</p> <p>6 individual patient's ovarian cancer; is that right?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A As a -- a radiologist, I do not.</p> <p>9 Q (BY MR. ZELLERS) You don't diagnose what</p> <p>10 caused any individual patient's ovarian cancer; is</p> <p>11 that right, in your practice -- your medical</p> <p>12 practice.</p> <p>13 MS. O'DELL: Objection, asked and</p> <p>14 answered.</p> <p>15 A I -- I -- I do not. I diagnose ovarian</p> <p>16 cancer. I diagnosis pelvic inflammatory disease.</p> <p>17 But in an individual patient, I wouldn't tell a</p> <p>18 patient why they got ovarian cancer.</p> <p>19 Q (BY MR. ZELLERS) You -- you have not, at</p> <p>20 least as of this time, published on your theory that</p> <p>21 there is a causal association between genital talcum</p> <p>22 powder exposure and ovarian cancer; is that right?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A I have not published on my conclusion that</p> <p>25 talcum powder products causes ovarian cancer.</p>	<p style="text-align: right;">Page 121</p> <p>1 right?</p> <p>2 A Had -- you're asking if I have written</p> <p>3 op-eds on areas I have done research?</p> <p>4 Q Yes.</p> <p>5 A Yes, I have.</p> <p>6 Q Back in 2014, you did an op-ed in The New</p> <p>7 York Times relating to CT scans; is that right?</p> <p>8 A Yes, I did.</p> <p>9 Q All right. You concluded or at least put</p> <p>10 in the op-ed, In 2007, CT scans will cause 29,000</p> <p>11 excess cancer cases and 14,500 excess deaths; is</p> <p>12 that right?</p> <p>13 A I don't have it in front of me. But it</p> <p>14 looks like you do, and so I'm going to guess that</p> <p>15 that's correct.</p> <p>16 Q Well, does that sound right to you?</p> <p>17 A It does sound right.</p> <p>18 Q You put in that editorial or op-ed that in</p> <p>19 your opinion, 3 percent to 5 percent of all future</p> <p>20 cancers may result from exposure to medical imaging</p> <p>21 such as CT scans; is that right?</p> <p>22 MS. O'DELL: And if you have a</p> <p>23 recollection and -- and you -- and your memory</p> <p>24 confirms those -- those facts, please feel free to</p> <p>25 testify to it. If you need to see the op-ed, then</p>

<p style="text-align: right;">Page 122</p> <p>1 I'm sure counsel would be willing to put it in front 2 of you.</p> <p>3 A That particular statistic, I don't have to 4 see. I know that static --</p> <p>5 Q (BY MR. ZELLERS) All right.</p> <p>6 A -- so yes.</p> <p>7 Q You are familiar with the Center for 8 Disease Control, correct?</p> <p>9 A Yes, I am.</p> <p>10 Q The CDC or Center for Disease Control is a 11 reputable organization; is that right?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A I think they're a very reputable 14 organization.</p> <p>15 Q (BY MR. ZELLERS) You have served on 16 several committees for the CDC in the past; is that 17 right?</p> <p>18 A I currently work on several committees 19 with them.</p> <p>20 Q Do the doctors and scientists in the CDC 21 work hard to protect women's health, based on your 22 experience?</p> <p>23 A Yes, they do.</p> <p>24 Q In forming your opinions in this case, did 25 you consider the risk factors that the CDC</p>	<p style="text-align: right;">Page 124</p> <p>1 of many pieces of information I used.</p> <p>2 Q (BY MR. ZELLERS) Are you aware that in 3 their patient-facing websites, as well as their 4 publicly available information about ovarian cancer, 5 the CDC does not identify perineal use of talcum 6 powder as a risk factor for ovarian cancer?</p> <p>7 A Yes, I do remember seeing that.</p> <p>8 Q You don't have any reason to believe that 9 the folks at the CDC have not kept up to date with 10 talc and ovarian cancer epidemiology, do you?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A I believe that the comprehensiveness of 13 the review that I did and the amount of time that I 14 put into this review, as I have in -- in many other 15 reviews, requires a very deep dive into the 16 literature.</p> <p>17 And I do not believe that the CDC has 18 funding or resources to do that kind of deep dive. 19 And so typically what they do is sort of review some 20 things that have been published. Most things, they 21 don't end up reviewing.</p> <p>22 And so I have no reason to believe anyone 23 at the CDC deliberately didn't do a comprehensive 24 review of the literature, but -- nor do I have any 25 evidence that they did a comprehensive review of the</p>
<p style="text-align: right;">Page 123</p> <p>1 recognizes for ovarian cancer?</p> <p>2 A From my report, I read an enormous number 3 of articles, and I spent considerably time 4 considering those articles from a data point of 5 view.</p> <p>6 And I did not, for the most part, weigh 7 other organization's summaries if they were not 8 quantitative and very explicit in what reviews they 9 did, what literature they included.</p> <p>10 And sometimes they -- organizations did do 11 that, but did not do nearly as -- a comprehensive 12 job. So I -- I would not have relied on any 13 professional organization's reviews unless they were 14 quantitative the way -- the way my own were?</p> <p>15 MR. ZELLERS: Move to strike as 16 nonresponsive.</p> <p>17 Q (BY MR. ZELLERS) Let me ask the question 18 again. In forming your opinions in this case, did 19 you consider the risk factors that the CDC 20 recognizing for ovarian cancer?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A I saw documents on their websites that 23 list risk factors, and no individual organization's 24 summaries, either for patients or for clinicians, 25 formed a very large piece of my opinion. It was one</p>	<p style="text-align: right;">Page 125</p> <p>1 literature.</p> <p>2 Q (BY MR. ZELLERS) Do you have any personal 3 knowledge one way or the other as to the extent of 4 the review of the science and literature that the 5 CDC did in compiling its list of risk factors for 6 ovarian cancer?</p> <p>7 A I --</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A -- I would have to refresh my memory by 10 looking at their -- their website and documents. If 11 you provided those, I could.</p> <p>12 Q (BY MR. ZELLERS) My question is: Do you 13 have any personal knowledge one way or the other as 14 to what the CDC has done with respect to a review of 15 the scientific literature in compiling its list of 16 risk factors for ovarian cancer?</p> <p>17 A I don't know offhand what they did. And I 18 don't recall when looking at their website, what 19 references they listed.</p> <p>20 I think if their reference list included a 21 very short -- small number of references, I would 22 have concluded that they had not done a very 23 comprehensive review.</p> <p>24 Q (BY MR. ZELLERS) My question is: Do you 25 have any personal knowledge as to what the CDC did</p>

<p style="text-align: right;">Page 126</p> <p>1 or did not do with respect to its review of the 2 literature?</p> <p>3 A Again, I don't know off the top of my 4 head. But I know I went to their website, and I 5 don't --</p> <p>6 Q Other than looking at their website, do 7 you have any personal knowledge?</p> <p>8 A No, I do not.</p> <p>9 Q All right. Have you communicated to 10 anyone at the CDC that you disagree with their 11 position?</p> <p>12 A I -- I'm laughing at the nature of the 13 question. There wouldn't be anyone at the CDC to 14 disagree with.</p> <p>15 Q There -- there's no one at the CDC that 16 you, as a concerned radiologist, could go to and 17 say: Hey, I think that you should list perineal 18 talc use as a risk factor for ovarian cancer?</p> <p>19 MS. O'DELL: Object to the form.</p> <p>20 Q (BY MR. ZELLERS) There's no one you could 21 talk to at the CDC about that?</p> <p>22 A I -- I would -- I would have to confirm 23 that that -- I have been -- I -- I study 24 environmental carcinogens.</p> <p>25 And you pointed out my New York Times</p>	<p style="text-align: right;">Page 128</p> <p>1 MS. O'DELL: Object to the form.</p> <p>2 A Naive to suggest that a single person 3 could just call them and say: I have looked at this 4 topic, and you should change what you are doing.</p> <p>5 Q (BY MR. ZELLERS) Are you familiar with the 6 National Institute of Health?</p> <p>7 A I am.</p> <p>8 Q You have received funding from the 9 National Institute of Health; is that right?</p> <p>10 A I have.</p> <p>11 Q Do you know that the National Institute of 12 Health does not list talc use as a risk factor for 13 ovarian cancer?</p> <p>14 MS. O'DELL: Object to form.</p> <p>15 A Again, I -- yeah, I know that the NCI, PDQ 16 that writes reports for patients and clinicians 17 about risk factors for cancer has a report on risk 18 factors for ovarian cancer and that they conclude 19 that there's inadequate evidence for talc.</p> <p>20 Q (BY MR. ZELLERS) Inadequate evidence, 21 correct?</p> <p>22 A I -- I -- I wasn't finished.</p> <p>23 Q Please finish.</p> <p>24 A So they don't stand -- just to clarify, 25 for the National Institute of Health. It's a very</p>
<p style="text-align: right;">Page 127</p> <p>1 op-ed that put a message out there that said: I 2 think this is an environmental carcinogen.</p> <p>3 And I have spoken about that topic in many 4 forms. I have testified before Congress several 5 times. I testified to the FDA. I have spoken to 6 CMS.</p> <p>7 All of that took years to get people to 8 hear those messages. It was not that: Oh, I see 9 there's a problem here. Let me just tell the top 10 person to do that.</p> <p>11 And -- and so I'm -- you're suggesting 12 there's someone at the CDC that I could call and 13 say: Oh, by the way, I think that's an important 14 topic. I appreciate your giving me that idea. I 15 will move forward once I publish a paper on this 16 topic.</p> <p>17 But -- but that's not nearly as -- as 18 simple as you're suggesting in your question. 19 There's a naiveness there that there's someone at 20 the CDC who would -- who takes responsibility for 21 what they do and -- on all of their websites and you 22 can sort of give them feedback on that.</p> <p>23 Q You believe I'm being naive to think that 24 there's a person responsible at the CDC for 25 compiling a list of risk factors for ovarian cancer?</p>	<p style="text-align: right;">Page 129</p> <p>1 prestige body. It's an organization within a small 2 part of the NCI.</p> <p>3 I know it well, because I served on that 4 committee for many years. I know the process 5 whereby they review the literature and created a 6 whole a bunch of standards within what they do 7 around that.</p> <p>8 And I looked and saw that they updated 9 their summary of talc in 2018. And -- and yet, 10 within that summary, they do list the references 11 that they cite, and they omit a large number of 12 references that are recent.</p> <p>13 So I do know their conclusion. I do not 14 agree with their conclusion. And there were large 15 gaps in their literature. And that update was very 16 recent.</p> <p>17 I -- I told you I don't know the 18 leadership at the CDC, and they don't have a 19 process. But I do know the leadership on this 20 committee and -- and will point out their omissions 21 to this committee.</p> <p>22 Q Well, I haven't gotten to the National 23 Cancer Institute yet.</p> <p>24 My question was: Do you know that NIH, 25 the National Institute of Health, does not list use</p>

<p style="text-align: right;">Page 130</p> <p>1 of talcum powder as a risk factor for ovarian 2 cancer? 3 A So I -- I -- I don't know what -- I'm 4 sorry. I don't know what you're talking about, 5 the -- 6 Q All right. 7 A -- NIH. 8 Q Take a look, if you will, at Deposition 9 Exhibit 19, which is captioned NIH steer -- or 10 "SEER, S E E R, Training Modules" and has got "Risk 11 Factors" at the top. 12 (Exhibit 19 was marked for identification 13 and is attached to the transcript.) 14 MS. O'DELL: Thank you. 15 A So SEER is also a part of National Cancer 16 Institute. It's the surveillance epidemiology -- 17 MR. LAPINSKI: Have her wait for a 18 question. 19 MS. O'DELL: Sorry. Just wait for his 20 question. Yeah, thanks, Dan. 21 Q (BY MR. ZELLERS) You recognize Exhibit 19 22 as a training module from NIH and specifically from 23 the National Cancer Institute; is that right? 24 A So this says at the top "SEER Training 25 Modules."</p>	<p style="text-align: right;">Page 132</p> <p>1 include modifiable and nonmodifiable parameters. 2 Is that right? And then it lists out 3 nonmodifiable parameters and modifiable parameters; 4 is that right? 5 A Yes, that's what this -- 6 Q Talcum -- 7 A -- says. 8 Q -- powder use is not listed, correct? 9 A Correct. 10 Q All right. Take a look, if you will -- 11 and this is the document that you were talking about 12 a moment ago -- at Deposition Exhibit 20. 13 (Exhibit 20 was marked for identification 14 and is attached to the transcript.) 15 Q (BY MR. ZELLERS) This is the "National 16 Cancer Institute Review of Ovarian, Fallopian Tube, 17 and Primary Peritoneal Cancer Prevention PDQ"; is 18 that right? 19 A Yes, it is. 20 Q This is the document that you told us a 21 few minutes ago that you disagree with the 22 conclusion; is that right? 23 And specifically if you go to page 5 of 9 24 under "Perineal Talc Exposure," the statement from 25 the National Cancer Institute in this document is</p>
<p style="text-align: right;">Page 131</p> <p>1 I don't know what this is. I know SEER 2 quite well. It's the National Cancer Registries. 3 But I -- I don't -- don't know what this training 4 module is. But I do see that you are showing me 5 some risk factors. 6 Q Talc is not listed as a risk factor for 7 ovarian cancer in this document, Exhibit 19, that 8 was updated in June of 2018 from NIH and the 9 National Cancer Institute; is that right? 10 A I -- I want to sort of explain my 11 confusion. The SEER, Surveillance, Epidemiology, 12 and End Result, program does not train or educate 13 individuals typically using documents like this. 14 Often this is for cancer abstractors to 15 know what information they're asking their 16 abstractors to collect. 17 I -- I don't know what this is, but it 18 doesn't look to me like something that's identifying 19 risk factors as much as asking medical chart 20 abstractors to write down information that they're 21 collecting as part of their data. 22 Q My question is very simple. This is a 23 list that at the top says "Risk Factors." 24 The introductory statement says, The main 25 risk and protective factors for ovarian cancers</p>	<p style="text-align: right;">Page 133</p> <p>1 that the weight of evidence does not support an 2 association between perineal talc exposure and an 3 increased risk of ovarian cancer. Results from 4 case-control and cohort studies are inconsistent. 5 Is that right? 6 A That is what they conclude. 7 Q This was updated, if you looked at the 8 last page, page 9 of 9, on January 4 of 2019; is 9 that right? 10 MS. O'DELL: Object to the form. 11 A Can you show me where it's been updated? 12 Q (BY MR. ZELLERS) Sure. Look at the very 13 last page. In bold, "Updated January 4, 2019"; is 14 that right? 15 A It does say that -- 16 Q All right. 17 A -- yes. 18 Q Are there limitations on epidemiological 19 data? 20 A Yes, there are. 21 Q Do you agree that epi -- epidemiologic 22 data alone cannot permit a determination regarding 23 causation? 24 A I'm sorry. Can you just -- 25 Q Do you need me to say it again or can you</p>

<p style="text-align: right;">Page 134</p> <p>1 read it off the screen?</p> <p>2 A I can read it off the screen. I think</p> <p>3 epidemiologic data can provide an enormous amount of</p> <p>4 information about causation. But there are other</p> <p>5 considerations that would have to be also taken into</p> <p>6 account to also support that.</p> <p>7 Q Can epidemiologic data alone permit a</p> <p>8 determination regarding causation?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A I think epidemiologic data can be used in</p> <p>11 combination with other data to determine causality,</p> <p>12 but by itself cannot be used alone to determine</p> <p>13 causality.</p> <p>14 Q (BY MR. ZELLERS) The current epidemiologic</p> <p>15 data, as it exists, does not enable someone to</p> <p>16 distinguish between brands of cosmetic talc</p> <p>17 products; is that right?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A I would agree.</p> <p>20 Q (BY MR. ZELLERS) You can't tell in any of</p> <p>21 the 40 plus studies that you reviewed, that the</p> <p>22 women who were involved in those studies used talc</p> <p>23 products manufactured by Johnson &amp; Johnson</p> <p>24 Consumer, Inc., or by another company; is that</p> <p>25 right?</p>	<p style="text-align: right;">Page 136</p> <p>1 awful lot of Johnson &amp; Johnson baby powder over the</p> <p>2 last 50 plus years. And -- and I am --</p> <p>3 Q (BY MR. ZELLERS) And --</p> <p>4 A -- not sure whether there's lots of other</p> <p>5 dominant players in the space. I -- I don't know</p> <p>6 that.</p> <p>7 My impression is that Johnson -- baby</p> <p>8 powder baby is a Johnson &amp; Johnson a product very,</p> <p>9 very often.</p> <p>10 Q But you have not done any type of survey</p> <p>11 --</p> <p>12 A I have --</p> <p>13 Q -- or analysis?</p> <p>14 A -- I have not.</p> <p>15 Q If the biological mechanism by which a</p> <p>16 talcum powder product can increase the risk of</p> <p>17 ovarian cancer is because of a particular</p> <p>18 contaminant or collection of contaminants, but that</p> <p>19 contaminant or collection of contaminants does not</p> <p>20 exist in all talcum powder products, will the</p> <p>21 epidemiologic evidence that exists today allow you</p> <p>22 to see that distinction?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A You're asking about contaminants of talcum</p> <p>25 powder products. My understanding from what I have</p>
<p style="text-align: right;">Page 135</p> <p>1 MS. O'DELL: Object to the form.</p> <p>2 A I -- I would agree that most of the papers</p> <p>3 that I read did not specify what the source of the</p> <p>4 baby powder was.</p> <p>5 Q (BY MR. ZELLERS) Based on the analysis</p> <p>6 that you have done, you're not able to draw an</p> <p>7 opinion specifically about an increased risk of</p> <p>8 ovarian cancer that is tied to a particular brand of</p> <p>9 talcum powder, correct?</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A My impression is that a large proportion</p> <p>12 of the talcum powder products that are available</p> <p>13 happen to be made by Johnson &amp; Johnson, but I do not</p> <p>14 know for any given study -- for most of the studies,</p> <p>15 at least, what kind of talcum powder it was.</p> <p>16 Q (BY MR. ZELLERS) Okay. Is your impression</p> <p>17 that you just shared with us, you know, based on</p> <p>18 information you have received from plaintiffs'</p> <p>19 counsel?</p> <p>20 MS. O'DELL: Object to the form. Don't --</p> <p>21 don't discuss what's been provided by -- let me say</p> <p>22 that again.</p> <p>23 Don't -- don't discuss conversations with</p> <p>24 plaintiffs' counsel. Thank you.</p> <p>25 A I -- my impression is based on seeing an</p>	<p style="text-align: right;">Page 137</p> <p>1 reviewed is that the components of talcum powder</p> <p>2 products include asbestos, include fibrous talc,</p> <p>3 include heavy metals, include fragrances.</p> <p>4 Let's get rid of the header -- the --</p> <p>5 the fragrances. Just the heavy metals, the</p> <p>6 asbestos, and the fibrous talc. My understanding is</p> <p>7 that those are in the same mines as the platy talc,</p> <p>8 which is the desired part of talc.</p> <p>9 To the degree that those are all part and</p> <p>10 parcel of the same product, they're not -- I</p> <p>11 wouldn't think of them as contaminants. I would</p> <p>12 think of them as just part of the product.</p> <p>13 And so to the degree that that product</p> <p>14 cannot be separated, I would be concerned that any</p> <p>15 talcum powder products have all of the above.</p> <p>16 I separated fragrance, because that's</p> <p>17 something that's added. That's not mined directly.</p> <p>18 But the other items, my understanding is that's part</p> <p>19 of the talc.</p> <p>20 Q You don't know one way or the other</p> <p>21 whether talcum powder products contain asbestos, do</p> <p>22 you?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A You're asking me to opine whether talcum</p> <p>25 powder products contain asbestos?</p>



<p style="text-align: right;">Page 138</p> <p>1 Q (BY MR. ZELLERS) Yes.</p> <p>2 A Yes, I -- I feel very certain that talcum</p> <p>3 powder products, at least over many years, contained</p> <p>4 asbestos.</p> <p>5 Q Is that part of your opinion in this case?</p> <p>6 A Yes, it is.</p> <p>7 Q Is it your opinion in this case that</p> <p>8 talcum powder products contain trace amounts of</p> <p>9 heavy metals?</p> <p>10 A Yes, it is.</p> <p>11 Q Is it also part of your opinion in this</p> <p>12 case that talcum powder products contain different</p> <p>13 fragrance chemicals?</p> <p>14 A Yes, it is.</p> <p>15 Q Do you have any opinion as to how many</p> <p>16 fragrance chemicals are contained in talcum powder</p> <p>17 manufactured by a Johnson &amp; Johnson company at any</p> <p>18 time?</p> <p>19 MS. O'DELL: Object to the form. With</p> <p>20 regard to "opinion."</p> <p>21 A I have seen long lists of chemicals and</p> <p>22 fragrances that are contained.</p> <p>23 I'm not familiar enough with -- with the</p> <p>24 testing that was done to understand how that's</p> <p>25 changed over time in a Johnson &amp; Johnson product</p>	<p style="text-align: right;">Page 140</p> <p>1 manufactured by Johnson &amp; Johnson?</p> <p>2 MS. O'DELL: Object to the form. to the</p> <p>3 form.</p> <p>4 A So unlike the question about heavy metals</p> <p>5 where it sort -- there are traces of heavy metals in</p> <p>6 other things to which we're exposed regularly, like</p> <p>7 water. We don't expect any concentrations of</p> <p>8 asbestos in products that we're exposed to.</p> <p>9 And so put in that context, while I'm not</p> <p>10 an expert in the mineralogy, the numbers that I have</p> <p>11 seen are tens of thousands to millions of fibers</p> <p>12 that might be in grams of product seem like an awful</p> <p>13 lot of units or dose of -- of asbestos or fibrous</p> <p>14 talc.</p> <p>15 MR. ZELLERS: Move to strike as</p> <p>16 nonresponsive.</p> <p>17 Q (BY MR. ZELLERS) You do not have personal</p> <p>18 knowledge as to any amounts or concentrations of</p> <p>19 asbestos in talcum powder manufactured by Johnson &amp;</p> <p>20 Johnson --</p> <p>21 MS. O'DELL: Objection.</p> <p>22 Q (BY MR. ZELLERS) -- correct?</p> <p>23 MS. O'DELL: Objection, asked and</p> <p>24 answered.</p> <p>25 A I have seen several reports of Johnson &amp;</p>
<p style="text-align: right;">Page 139</p> <p>1 versus other talcum powder products.</p> <p>2 Q (BY MR. ZELLERS) Do you have any opinion</p> <p>3 or knowledge as to the amount or concentration of</p> <p>4 particular fragrance chemicals that are contained in</p> <p>5 talcum powder manufactured by Johnson &amp; Johnson?</p> <p>6 A I -- I do not.</p> <p>7 Q Do you have any opinion or knowledge as to</p> <p>8 the amount or concentration of trace chemicals</p> <p>9 -- strike that -- trace heavy metals that may be</p> <p>10 contained in talcum powder manufactured by Johnson &amp;</p> <p>11 Johnson?</p> <p>12 A I have seen reports of the amounts that --</p> <p>13 you know, sort of in the ballpark of hundreds to</p> <p>14 thousands of parts per million.</p> <p>15 But I'm not an expert in understanding</p> <p>16 those numbers in comparison to the concentrations in</p> <p>17 other things that we're exposed to. They're much</p> <p>18 higher. They're orders of magnitudes higher, but</p> <p>19 I'm not an expert to understand how those different</p> <p>20 concentrations might be expected to have an</p> <p>21 influence on talc.</p> <p>22 Q The same question with respect to</p> <p>23 asbestos. Do you have any opinion or knowledge as</p> <p>24 to the amount or concentration of asbestos that you</p> <p>25 believe is contained in any talcum powder</p>	<p style="text-align: right;">Page 141</p> <p>1 Johnson products that have been tested for</p> <p>2 concentrations of asbestos or asbestiform talc that</p> <p>3 have concentrations shown kind of in ranges of a</p> <p>4 tenth of a percent or, as I mentioned, tens of</p> <p>5 thousands or mid -- millions of fibers.</p> <p>6 And those have been tested by -- by</p> <p>7 several different people, but coming up with units</p> <p>8 of dose within Johnson &amp; Johnson talcum powder</p> <p>9 products.</p> <p>10 Q (BY MR. ZELLERS) You're not a geologist,</p> <p>11 correct?</p> <p>12 A I am not a geo --</p> <p>13 Q You're --</p> <p>14 A -- logist.</p> <p>15 Q -- not a mineralogist, correct?</p> <p>16 A I am not.</p> <p>17 Q You have reviewed some expert reports from</p> <p>18 Dr. Longo; is that right?</p> <p>19 A Among others, yes.</p> <p>20 Q You have reviewed some testing reports.</p> <p>21 Some purportedly show that there is asbestos present</p> <p>22 in talcum powder and some that show that there's not</p> <p>23 asbestos in talcum powder; is that right?</p> <p>24 MS. O'DELL: Object to the form.</p> <p>25 A I have seen a lot of reports that have</p>



<p style="text-align: right;">Page 142</p> <p>1 shown the presence of talcum powder containing</p> <p>2 asbestos and fibrous talc.</p> <p>3 You listed some of those, the Longo</p> <p>4 reports, a bunch of publications in the literature</p> <p>5 such as Blount's.</p> <p>6 I have seen some testing from Dr. Hopkins,</p> <p>7 from Imerys, from Cooke. I have also seen some</p> <p>8 negative reports.</p> <p>9 Q (BY MR. ZELLERS) The answer to my question</p> <p>10 is: Yes, you have seen testing that purportedly</p> <p>11 shows there to be some asbestos in the J&amp;J</p> <p>12 manufactured talcum powder and you have seen reports</p> <p>13 that, you know, indicate there's not asbestos in the</p> <p>14 talcum powder; is that fair?</p> <p>15 A The way that you have described it makes</p> <p>16 it seem like I have seen comprehensive reports that</p> <p>17 have shown in totality there is asbestos and reports</p> <p>18 that have shown there's not. I haven't seen that.</p> <p>19 Q All right.</p> <p>20 A I have seen reports that have shown in</p> <p>21 totality there are. I have seen individual samples</p> <p>22 that have shown there's not asbestos in those</p> <p>23 individual samples.</p> <p>24 But I haven't seen a systematic report</p> <p>25 that have shown in, for example, a large number of</p>	<p style="text-align: right;">Page 144</p> <p>1 off the record for a moment.</p> <p>2 THE VIDEOGRAPHER: We're off the record at</p> <p>3 1:36 p.m.</p> <p>4 (A break was taken from 1:36 p.m. to</p> <p>5 1:37 p.m.)</p> <p>6 THE VIDEOGRAPHER: We are back on the</p> <p>7 record. The time is 1:37 p.m.</p> <p>8 Q (BY MR. ZELLERS) Dr. Smith-Bindman, you</p> <p>9 had recalled, I believe, the name of the fourth</p> <p>10 plaintiff lawyer that you met with?</p> <p>11 A Carmen Scott.</p> <p>12 Q I want to ask you some questions about the</p> <p>13 systematic review that you did. You have not</p> <p>14 published that, correct?</p> <p>15 A I have not.</p> <p>16 Q If at any point you do publish your</p> <p>17 systematic review, would you disclose that you are a</p> <p>18 paid expert for the Plaintiffs in the talcum powder</p> <p>19 litigation?</p> <p>20 A Yes, I would.</p> <p>21 Q You would expect any expert who is paid to</p> <p>22 perform a review or who has a study funded by</p> <p>23 Plaintiffs to make that disclosure, correct?</p> <p>24 MS. O'DELL: Object to the form.</p> <p>25 A My understanding from my experience is</p>
<p style="text-align: right;">Page 143</p> <p>1 specimens, none had asbestos. I haven't seen that.</p> <p>2 Q You have seen, at least in large part, the</p> <p>3 information that's been provided to you by</p> <p>4 plaintiffs' attorneys; is that right?</p> <p>5 MS. O'DELL: Object to the form. to the</p> <p>6 form.</p> <p>7 A I think some of the public -- published</p> <p>8 literature was not provided by plaintiff attorneys</p> <p>9 and some has been, such as the Longo reports.</p> <p>10 MR. ZELLERS: All right.</p> <p>11 MS. O'DELL: Mike, we have been going</p> <p>12 about an hour and 30 minutes. And our lunch is</p> <p>13 here, so is this a good time.</p> <p>14 MR. ZELLERS: Sure --</p> <p>15 MS. O'DELL: -- for a break?</p> <p>16 MR. ZELLERS: -- of course.</p> <p>17 THE VIDEOGRAPHER: This marks the end of</p> <p>18 Disc 2. We are off the record at 12:37 p.m.</p> <p>19 (A break was taken from 12:37 p.m. to</p> <p>20 1:36 p.m.)</p> <p>21 THE VIDEOGRAPHER: We are back on the</p> <p>22 record. This marks the beginning of Disc No. 3 in</p> <p>23 the deposition of Dr. Rebecca Smith-Bindman. The</p> <p>24 time is 1:36 p.m.</p> <p>25 MR. ZELLERS: Dr. Smith-Bindman, let's go</p>	<p style="text-align: right;">Page 145</p> <p>1 that different journals require different</p> <p>2 disclosures. So if you're paid by someone, you</p> <p>3 typically would have to disclose, but the detail</p> <p>4 would -- would vary by journal.</p> <p>5 Q (BY MR. ZELLERS) What methodology or</p> <p>6 methodologies did you use to arrive at your opinion</p> <p>7 that regular use of talcum powder increases a</p> <p>8 woman's risk of developing invasive serous cancer by</p> <p>9 about 50 percent?</p> <p>10 A So I would say there were two parts. The</p> <p>11 first part is my systematic review of the published</p> <p>12 literature. I think I mentioned earlier that I have</p> <p>13 published several systematic reviews.</p> <p>14 And the mechanism of perform -- performing</p> <p>15 those systematic reviews are both ones that I have</p> <p>16 personally used and ones that I was involved in</p> <p>17 developing the methodology as part of my work on the</p> <p>18 Cochrane collaboration.</p> <p>19 So it involves doing a very standardized</p> <p>20 search, creating an approach for abstracting data,</p> <p>21 abstracting the data. An approach that I used for</p> <p>22 summarizing the data, which usually is looking at</p> <p>23 stratified results, results in sort of specific</p> <p>24 categories as opposed to broad categories.</p> <p>25 Statistically summarizing the results and showing</p>

<p style="text-align: right;">Page 146</p> <p>1 them.</p> <p>2 So part of my conclusion was based on my</p> <p>3 own systematic review. And then part of my</p> <p>4 conclusion was based on my review of the published</p> <p>5 literature on the actual epidemiology data, as well</p> <p>6 as other considerations that went into consideration</p> <p>7 of the Bradford Hill criteria such as mechanistic</p> <p>8 data and any other requirements of Bradford Hill.</p> <p>9 Q Tell us step by step how you performed</p> <p>10 your systematic review or analysis. And now I'm</p> <p>11 referring to the meta-analysis or meta-analysis-like</p> <p>12 review that you did.</p> <p>13 A Okay. So I would just like to do a slight</p> <p>14 preamble to that, which is that the direction that</p> <p>15 my review took was partly informed by having read</p> <p>16 through a number of articles on the topic. So</p> <p>17 determining sort of where there was a gap, what was</p> <p>18 the most important area to focus on. So that sort</p> <p>19 of was the background.</p> <p>20 And then for the review, the literature</p> <p>21 search is the first step. So you want to broadly</p> <p>22 identify all relevant literature, published and</p> <p>23 unpublished, to include.</p> <p>24 And that includes searching on several</p> <p>25 databases -- PubMed was -- Medline were -- Embase,</p>	<p style="text-align: right;">Page 148</p> <p>1 through those and to review to make sure that they</p> <p>2 had primary data.</p> <p>3 So I was only interested in studies that</p> <p>4 had primary data, which meant that review articles</p> <p>5 or editorials or letters to the editors or opinion</p> <p>6 pieces were dropped from that list.</p> <p>7 So then I had data that were -- I had</p> <p>8 studies that had primary data, so that became my</p> <p>9 list of articles.</p> <p>10 And -- and then I created a data</p> <p>11 abstraction form for what variables I wanted to</p> <p>12 include. So some variables are the number of cases;</p> <p>13 the number of controls; the kind of study design</p> <p>14 whether it was a case-control study or another</p> <p>15 design.</p> <p>16 It included -- included the groups that I</p> <p>17 cared most about. So you mentioned serous cancer,</p> <p>18 so I included what kind of histologies they looked</p> <p>19 at.</p> <p>20 I included in my initial data form,</p> <p>21 variables that I ended up not using in my review</p> <p>22 because I didn't have enough data.</p> <p>23 So in my initial draft of variables that I</p> <p>24 might like to abstract was the relationship in pre</p> <p>25 versus postmenopausal women.</p>
<p style="text-align: right;">Page 147</p> <p>1 Scopus were -- were databases that I started my</p> <p>2 search.</p> <p>3 I included in the report some of the</p> <p>4 keywords I used, keywords including "ovarian cancer,</p> <p>5 talc, perineal powder, genital powder."</p> <p>6 So I generated a long list of articles</p> <p>7 that I retrieved and then reviewed the references</p> <p>8 for each of those articles, which usually doesn't</p> <p>9 identify a lot more articles, but usually identifies</p> <p>10 a few that I may have missed in my search, but that</p> <p>11 other people have found in their reviews or</p> <p>12 systematic reviews. So the first step was to</p> <p>13 identify the literature.</p> <p>14 Q What was the next step? And again, I'm</p> <p>15 focused on your methodology for the systematic</p> <p>16 review or analysis that you did, as reflected in</p> <p>17 your report?</p> <p>18 A So the second step is: Identified a large</p> <p>19 number of publications, but some of them may not</p> <p>20 have been particularly relevant.</p> <p>21 For example, they may have sounded in the</p> <p>22 title like they were primary data, but they may have</p> <p>23 actually only been review data.</p> <p>24 So Step 2 is to review the abstracts for</p> <p>25 all of those identified articles and then to go</p>	<p style="text-align: right;">Page 149</p> <p>1 But when I ended up reviewing articles,</p> <p>2 there just was not -- not enough data there to make</p> <p>3 sense of, so I created a data abstraction form.</p> <p>4 I then went one by one through the</p> <p>5 articles which I organized and abstracted the data</p> <p>6 that I had set out to do.</p> <p>7 And in the course of doing that, I would</p> <p>8 ensure that the participants that were described in</p> <p>9 those reports were, in fact, unique subjects.</p> <p>10 So within this field, just like many</p> <p>11 fields, people sometimes publish an individual</p> <p>12 patient in more than one study. And -- and you</p> <p>13 don't want to include that, if you can.</p> <p>14 So as part of my review was to determine</p> <p>15 how independent the patients were and to make a note</p> <p>16 if there was overlap.</p> <p>17 I also didn't mention some of the features</p> <p>18 that I abstracted. But it wasn't just the primary</p> <p>19 result, which was what was the adjusted odds ratio</p> <p>20 or risk ratio associated with exposure to talcum</p> <p>21 powder products, but it was also -- what I was most</p> <p>22 interested in is quantifying that exposure to a</p> <p>23 degree that had not been present in all the</p> <p>24 individual reviews that I had previously said. So I</p> <p>25 was interested primarily in abstracting data on</p>

<p style="text-align: right;">Page 150</p> <p>1 regular exposure to talcum powder.</p> <p>2       So when I went through the articles, I</p> <p>3 noted whether -- what the point estimates were, but</p> <p>4 also whether they had information on all of the</p> <p>5 things that were in my database.</p> <p>6       I went through and abstracted data several</p> <p>7 times.</p> <p>8       Q   Okay. Well, that's --</p> <p>9       A   Oh.</p> <p>10       MS. O'DELL: She may not be done but --</p> <p>11       Q   (BY MR. ZELLERS) Well, I understand. So</p> <p>12 I'm just trying to go through your methodology here.</p> <p>13       So after you abstracted the data and</p> <p>14 included it or put it on your data abstraction form</p> <p>15 for each study, what was the next step in your</p> <p>16 systematic review?</p> <p>17       MS. O'DELL: So just continue on, Doctor,</p> <p>18 what your process was.</p> <p>19       A   Okay. Well -- so the next step was to</p> <p>20 decide which -- which of those papers might have</p> <p>21 been missing data.</p> <p>22       So once I abstracted the data, there were</p> <p>23 gaps almost certainly in the data. And so I -- I</p> <p>24 just wanted to emphasize -- I was starting to say</p> <p>25 this earlier -- that I -- I went back to the papers</p>	<p style="text-align: right;">Page 152</p> <p>1       Q   That's what Dr. Hall did; is that right?</p> <p>2       A   That is what Dr. Hall did. I should have</p> <p>3 a caveat there. We -- she absolutely lead that part</p> <p>4 of the analysis, but I reviewed every step of that</p> <p>5 very carefully.</p> <p>6       And there were several places that I --</p> <p>7 I -- I saw errors in some of the calculations that</p> <p>8 we went back and forth on to correct those</p> <p>9 calculation errors.</p> <p>10       Q   Have you completed your methodology or the</p> <p>11 different steps in your methodology?</p> <p>12       MS. O'DELL: In terms of the</p> <p>13 meta-analysis?</p> <p>14       Q   (BY MR. ZELLERS) Yes. In terms of the</p> <p>15 systematic review or meta-analysis that you did.</p> <p>16       A   I believe I have highlighted all the</p> <p>17 steps.</p> <p>18       Q   You tried or did correct any errors in</p> <p>19 calculations or numbers by Dr. Hall; is that right?</p> <p>20       MS. O'DELL: Object to the form.</p> <p>21       A   Yes, I did.</p> <p>22       Q   (BY MR. ZELLERS) Did anyone else review</p> <p>23 your calculations and Dr. Hall's calculations?</p> <p>24       A   No. Just the two of us.</p> <p>25       You said something, that I corrected some</p>
<p style="text-align: right;">Page 151</p> <p>1 and tried to sort of ensure that I was consistently</p> <p>2 pulling the data in my database requirement for</p> <p>3 every study.</p> <p>4       After I did that, the next step would be</p> <p>5 to combine the data statistically. And that would</p> <p>6 be to pro -- perform steps to figure out how the</p> <p>7 data can be -- could be combined.</p> <p>8       And that required looking at issues of</p> <p>9 consistency across the studies or heterogeneity and</p> <p>10 then to make sure that the sub analysis that I</p> <p>11 wanted to do -- the stratified analysis that I</p> <p>12 wanted to do could be done based on whether I had</p> <p>13 data for each of those studies in the stratified</p> <p>14 category.</p> <p>15       So as an example, I wanted to make sure</p> <p>16 that I -- I had whatever information was in the</p> <p>17 paper that could then go to the next step of</p> <p>18 analysis.</p> <p>19       And so that's when, actually, I reached</p> <p>20 out to a biostatistician with -- expert in the</p> <p>21 biostatistical aspect to do two things: To both</p> <p>22 double-check my numbers and ensure that the numbers</p> <p>23 that -- had been abstracted correctly and then to do</p> <p>24 the biostatistical analysis and generate the</p> <p>25 graphical representation of the data.</p>	<p style="text-align: right;">Page 153</p> <p>1 of her numbers. I -- she also corrected some of my</p> <p>2 numbers.</p> <p>3       It was a bi-directional two set of eyes on</p> <p>4 all of the analysis --</p> <p>5       Q   I --</p> <p>6       A   -- and abstractions.</p> <p>7       Q   -- essentially what you did is you</p> <p>8 analyzed the studies. You abstracted data on each</p> <p>9 of the studies on your Data Abstraction Form,</p> <p>10 correct?</p> <p>11       A   Yes.</p> <p>12       Q   Have you produced your Data Abstraction</p> <p>13 Forms to us for review?</p> <p>14       A   I -- I believe I have.</p> <p>15       Q   All right. You have them available; is</p> <p>16 that right?</p> <p>17       A   Yes.</p> <p>18       Q   And this would be a form for each of the</p> <p>19 studies in which you went through and you abstracted</p> <p>20 data; is that right?</p> <p>21       A   It's --</p> <p>22       MS. O'DELL: Object to the form. Sorry.</p> <p>23 Go ahead.</p> <p>24       A   -- yeah, it's -- it's an electronic</p> <p>25 database. It's an Excel file.</p>

<p style="text-align: right;">Page 154</p> <p>1 Q (BY MR. ZELLERS) But there would be a form</p> <p>2 or an Excel sheet for each of the studies where you</p> <p>3 abstracted the data; is that right?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A There's an Excel sheet with each study</p> <p>6 listed as a separate line of data and many, many</p> <p>7 rows -- columns for each -- it's not a physical</p> <p>8 piece of paper and...</p> <p>9 Q (BY MR. ZELLERS) But it's something that</p> <p>10 could be printed out; is that right?</p> <p>11 A Yes.</p> <p>12 Q All right. Did you develop any type of</p> <p>13 protocol setting forth the different steps that you</p> <p>14 followed to do your systematic analysis that you</p> <p>15 have told us about?</p> <p>16 A The protocol that I followed for these</p> <p>17 steps is a very well-established, well-published --</p> <p>18 including by myself from any prior reviews --</p> <p>19 protocols.</p> <p>20 Q My question is: Did you write down</p> <p>21 anywhere, the protocol that you followed for doing</p> <p>22 this particular systematic review?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A I did not specifically write down for this</p> <p>25 review that I would do a literature search or</p>	<p style="text-align: right;">Page 156</p> <p>1 times week or more as possible and that I would</p> <p>2 focus on invasive serous cancer wherever possible.</p> <p>3 And so if that -- if that's what you mean</p> <p>4 by my "protocol," then yes, that was written down</p> <p>5 ahead of time.</p> <p>6 Q (BY MR. ZELLERS) I'm confused. Do you</p> <p>7 define -- well -- and No. 1, did you produce that</p> <p>8 protocol?</p> <p>9 A So I have -- I have my notes and -- which</p> <p>10 was part of the documents that you saw earlier</p> <p>11 today.</p> <p>12 Q The notes, you would describe as your</p> <p>13 protocol or an outline of your methodology?</p> <p>14 A Yes.</p> <p>15 Q All right. We'll mark your notes, which</p> <p>16 are your protocol, as Exhibit 21.</p> <p>17 (Exhibit 21 was marked for identification</p> <p>18 and is attached to the transcript.)</p> <p>19 Q (BY MR. ZELLERS) And it's just the one</p> <p>20 side sheet; is that right?</p> <p>21 A I believe I provided other documents in</p> <p>22 the datasheet that also has the notes of what group</p> <p>23 I was focusing on in e-mails that I have sent you.</p> <p>24 Q That would be other materials that you</p> <p>25 have produced; is --</p>
<p style="text-align: right;">Page 155</p> <p>1 abstract data and record points and then do the</p> <p>2 analysis.</p> <p>3 Q (BY MR. ZELLERS) What you have done in</p> <p>4 your systematic review is a subgroup analysis of</p> <p>5 those studies that you thought should be included;</p> <p>6 is that fair?</p> <p>7 A I call it a stratified analysis rather</p> <p>8 than a subgroup analysis. Usually a subgroup</p> <p>9 analysis is usually used to describe only limiting</p> <p>10 to certain groups of patients as opposed to some</p> <p>11 questions. So I -- I'm not sure that there's a</p> <p>12 distinction but...</p> <p>13 Q Well, you -- whether we call it a subgroup</p> <p>14 or whether we call it a stratified analysis, you</p> <p>15 went through the studies to try to find the studies</p> <p>16 that would give you information on women who were</p> <p>17 regular users, as you defined "regular users," and</p> <p>18 who developed invasive serous ovarian cancer,</p> <p>19 correct?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A Yes, that's what I did.</p> <p>22 When you asked about whether I have a</p> <p>23 protocol written down, I have written that I was</p> <p>24 going to abstract information about regular use of</p> <p>25 talc powder products defined as closely as three</p>	<p style="text-align: right;">Page 157</p> <p>1 A That's --</p> <p>2 Q -- the right?</p> <p>3 A -- correct.</p> <p>4 Q To your knowledge, there's nothing that</p> <p>5 you have not produced --</p> <p>6 A No.</p> <p>7 Q -- relating -- hold --</p> <p>8 A Okay.</p> <p>9 Q -- on. Let me finish.</p> <p>10 There's nothing, to your knowledge, that</p> <p>11 you have not produced relating to your analysis; is</p> <p>12 that right?</p> <p>13 A That's correct.</p> <p>14 Q I was confused. I thought you stated a</p> <p>15 moment ago that you defined "regular use" as the use</p> <p>16 of talcum powder three times a week or more.</p> <p>17 Is that your definition of "regular use"?</p> <p>18 A I --</p> <p>19 MS. O'DELL: Object to the form.</p> <p>20 A -- I describe the definition in my report</p> <p>21 on page 32. And --</p> <p>22 Q (BY MR. ZELLERS) My question just is: Is</p> <p>23 that the correct definition or did you use a</p> <p>24 different definition of "regular use"?</p> <p>25 MS. O'DELL: Object to the form. You may</p>

<p style="text-align: right;">Page 158</p> <p>1 describe your --</p> <p>2 A So I -- I --</p> <p>3 MS. O'DELL: -- definition.</p> <p>4 A -- have listed how I have defined it. And</p> <p>5 it's a little bit more -- more nuanced than what you</p> <p>6 have just asked me to confirm.</p> <p>7 Q (BY MR. ZELLERS) What is your definition</p> <p>8 of "regular use" with respect to the systematic</p> <p>9 review and analysis that you did?</p> <p>10 A So I have written, Regular use was defined</p> <p>11 ideally as daily or at least more than three uses</p> <p>12 per week.</p> <p>13 Q More than three uses a week; is that</p> <p>14 right?</p> <p>15 A I -- I wasn't finished. May I finish?</p> <p>16 Q Sure.</p> <p>17 A "I also accepted studies that defined</p> <p>18 "use" as regular where the description made it clear</p> <p>19 that this was regular use.</p> <p>20 A study that reported regular use, but</p> <p>21 defined it as less -- as used less frequency --</p> <p>22 at -- use of less than as -- frequency were not</p> <p>23 included.</p> <p>24 Regular use was selected to differentiate</p> <p>25 occasional use, which may include one-time</p>	<p style="text-align: right;">Page 160</p> <p>1 A -- page --</p> <p>2 MS. O'DELL: -- go ahead.</p> <p>3 A -- 32.</p> <p>4 Q (BY MR. ZELLERS) You have defined "regular</p> <p>5 use" in your report on page 32; is that right?</p> <p>6 A Yes.</p> <p>7 Q What is Dr. Hall's field of expertise?</p> <p>8 A She is a biostatistician who is -- does a</p> <p>9 lot of summaries of systematic review.</p> <p>10 Q You are not a biostatistician; is that</p> <p>11 right?</p> <p>12 A I did a two-year post-graduate fellowship</p> <p>13 in the Department of Epidemiology and Biostatistics,</p> <p>14 have taken many courses in biostatistician --</p> <p>15 biostatistics, and have thought classes in biostatistics</p> <p>16 --</p> <p>17 Q Do you con --</p> <p>18 A -- statistics.</p> <p>19 Q -- do you consider yourself to be an</p> <p>20 expert biostatistician?</p> <p>21 A I consider myself an expert in</p> <p>22 biostatistics.</p> <p>23 Q And Dr. Hall is also an expert in</p> <p>24 biostatistics; is that right?</p> <p>25 A Yes.</p>
<p style="text-align: right;">Page 159</p> <p>1 infrequent use or used along a particular time of a</p> <p>2 woman's menstrual cycle from sustained use.</p> <p>3 Studies that ask participants a single</p> <p>4 question about every use of talc without further</p> <p>5 quantification of exposure were not included for the</p> <p>6 summary.</p> <p>7 For example, Perdue reported that 52 to</p> <p>8 57 percent of women ever using talc without further</p> <p>9 quantification was not included."</p> <p>10 THE COURT REPORTER: Please slow down.</p> <p>11 Q (BY MR. ZELLERS) Okay.</p> <p>12 A Yes.</p> <p>13 Q Doctor, I just wanted to know your</p> <p>14 definition of "regular use."</p> <p>15 A I -- I -- I have spent considerable time</p> <p>16 both writing my definition and applying it to --</p> <p>17 Q What --</p> <p>18 A -- the papers.</p> <p>19 Q -- what page --</p> <p>20 MS. O'DELL: Excuse me, sir. If you were</p> <p>21 asking for the page, she can direct you to the page</p> <p>22 --</p> <p>23 Q (BY MR. ZELLERS) What page --</p> <p>24 A So --</p> <p>25 MS. O'DELL: Doctor --</p>	<p style="text-align: right;">Page 161</p> <p>1 Q Do you know -- well, did you conduct your</p> <p>2 systematic review and analysis using the PRISMA</p> <p>3 standards?</p> <p>4 A Yes.</p> <p>5 Q And those are the preferred reporting</p> <p>6 items for systematic reviews and meta-analyses; is</p> <p>7 that right?</p> <p>8 A Yes.</p> <p>9 Q What materials did you provide to Dr. Hall</p> <p>10 to assist you with your review?</p> <p>11 A I provided her with the data abstraction</p> <p>12 table that had information about each of the</p> <p>13 included studies.</p> <p>14 Q The data abstraction table that you</p> <p>15 prepared; is that right?</p> <p>16 A Yes.</p> <p>17 Q What specifically did Dr. Hall do to</p> <p>18 assist you?</p> <p>19 A She did two things. She personally</p> <p>20 reabstracted data from all of the publications.</p> <p>21 Most of those publications she found on her own.</p> <p>22 But for a couple, she was not able to find them, and</p> <p>23 I provided electronic versions of them.</p> <p>24 And then she statistically combined and</p> <p>25 compared the study to assess for heterogeneity to</p>



<p style="text-align: right;">Page 162</p> <p>1 calculate forest plots and summary-weighted 2 estimates. 3 Q What could Dr. Hall do with respect to 4 your analysis that you could not? 5 A I did not know how to use the software to 6 generate the graphs. And I thought that by the time 7 I learned how to use that software, it would be a 8 lot more efficient for her to generate them. 9 Q What did you do to check Dr. Hall's work 10 to make sure it was accurate? 11 A Dr. Hall sent me back my data abstraction 12 database where she had double-checked all of my 13 numbers and sent -- I think there were several data 14 points where she had questions about either whether 15 I abstracted the right number or put it in the right 16 category. 17 And of all of the items that she had 18 suggestions -- I think it was a small number -- I 19 went back to the original article to -- to confirm 20 or refute whether I agreed with her changes or not. 21 Sort of a way to -- by consensus to decide what the 22 right answer was. That was part of what I did. I 23 -- 24 Q How -- did you finish? 25 A -- no.</p>	<p style="text-align: right;">Page 164</p> <p>1 A I would not do it in that order. I -- I 2 generated the research questions first. 3 Q (BY MR. ZELLERS) You generated the 4 research questions after doing the initial 5 literature review you told us about this morning, 6 correct? 7 A I -- 8 MS. O'DELL: Object to the form. 9 A -- yes. 10 Q (BY MR. ZELLERS) All right. You 11 identified ten studies that discuss what you define 12 as "regular talc powder product use and risk of 13 ovarian cancer," and those are what you list on a 14 page 33 of your report; is that right? 15 A That's close to correct. I would include 16 in that another study, the Terry study, which is a 17 large study that pulls data from a bunch of other 18 component studies -- you can see on the top of 19 page 34 -- whether or not Terry was included or 20 excluded. The results were basically identical. 21 Q I'm just looking at your report. Your 22 report, on page 33, in Figure 2, you identify ten 23 studies that discuss what you define as "regular 24 talc powder product use and risk of ovarian cancer," 25 correct?</p>
<p style="text-align: right;">Page 163</p> <p>1 Q All right. Well, finish. 2 A She also generated -- she -- we went back 3 and forth. She had a bunch of questions. 4 But she also generated summary estimates. 5 And there were a bunch of categories that I asked 6 her to do. Some of those summary estimates, to me, 7 seemed like they didn't totally make essence. 8 So one analysis used seven studies and one 9 used nine, but it had the same final odds ratio out 10 to three digits. And it should have been the same 11 result perhaps, but not out to three digits. 12 So I went through those and sort of said: 13 Look, can you redouble-check this to make sure that 14 the weighting was correct? 15 And in one or two cases she came back and 16 said: No, the weighting was not correct. 17 So I rechecked every graph and every 18 number that she generated. 19 Q Ultimately, you identified -- let me 20 withdraw that. 21 You reviewed the studies; you did your 22 data abstraction; and you formulated your research 23 question or questions for the systematic review, 24 correct? 25 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 165</p> <p>1 MS. O'DELL: Object to the form. 2 A So that -- that paragraph is continued on 3 page 34, the next page at the top which says, The 4 primary analysis of this excluded Terry, but the 5 results were nearly identical if Terry was included. 6 Q (BY MR. ZELLERS) You could have included 7 Terry as part of Figure 2, and that would have been 8 an 11th study; is that right? 9 A Yes, that's correct. 10 Q Why did you not include Terry in your 11 analysis and -- in Figure 2? 12 A Terry included, within its -- within her 13 assembled papers, other patients that are already 14 included in Figure 2. 15 And including Terry would have listed -- 16 would have weighted some patients more than once. 17 Q Is there, to your knowledge, any 18 duplication or overlap in the patients for the ten 19 studies that you list in Figure 2 on page 33 of your 20 report? 21 A To the degree that I could eliminate 22 overlap, I did. 23 Q Is there overlap in some of the patients 24 and some of the studies? 25 A I would have to look at it again to remind</p>



<p style="text-align: right;">Page 166</p> <p>1 myself if there is any overlap. I -- I don't  2 believe there is.  3 And any overlap, I made every effort to  4 get rid of. I would have to look at those papers a  5 little bit more closely to remember if there was any  6 overlap.  7 I -- I know there was a lot of overlap if  8 I included Terry, which is why that was an important  9 exclusion.  10 Q How did you identify these ten studies  11 that you list in Figure 2?  12 A So I -- I did not identify those studies.  13 That was what -- Dr. Hall used the data that I  14 provided -- to identify which studies had the -- the  15 appropriate data to look at -- look at this.  16 Q How did Dr. Hall identify these ten  17 studies as being the ones to include in Figure 2?  18 A These were the studies that had data on  19 daily talc powder -- powder products.  20 Q You only used subsets of data from these  21 ten studies -- those ten studies listed in  22 Figure 2 -- to reach your conclusions, correct?  23 MS. O'DELL: Object to the form.  24 A I don't remember offhand if I used all of  25 the data from these studies or subsets of data from</p>	<p style="text-align: right;">Page 168</p> <p>1 A I -- I would not -- the individual studies  2 are shown with the confidence interval around those  3 point estimates.  4 One way to establish statistical  5 significance is -- is that statistically different  6 within an individual study than one.  7 But I don't believe that only two of these  8 show statistical significance as a group of studies.  9 So if you're asking if two don't overlap one, then I  10 would agree with you. If you're asking if these  11 together show statistical --  12 Q (BY MR. ZELLERS) I'm going to ask you --  13 MS. O'DELL: Excuse me. Sorry. Let her  14 finish. Sorry.  15 Q (BY MR. ZELLERS) Did you finish?  16 A I -- I'm trying to understand if you're  17 asking me if the original studies here show -- or  18 if -- just each line by itself.  19 Q If we go line by line for these ten  20 studies, only two of these ten studies demonstrate  21 statistical significance; is that right?  22 A Yes.  23 Q Yet you conclude by looking at all ten of  24 the studies that there is statistical significance;  25 is that right?</p>
<p style="text-align: right;">Page 167</p> <p>1 these studies to reach my conclusion.  2 There were only data from these ten  3 studies included in this figure, but I'm not sure if  4 I used all of the data from those studies or  5 subsets, as you asked.  6 Q (BY MR. ZELLERS) Would you agree that only  7 two of the ten studies in Figure 2 demonstrates  8 statistical significance?  9 A I would agree that taken altogether, these  10 studies show statistical significance. But I think  11 you're asking if they weren't taken together, if the  12 original studies were used, would those individual  13 studies show statistical significance? Is that what  14 you are asking?  15 Q No. You have listed out ten studies in  16 Figure 2; is that correct?  17 A Yes.  18 Q You are not aware whether you used all of  19 data from those studies for your systematic review  20 and analysis or subsets of the data, correct?  21 MS. O'DELL: Object to the form.  22 A Yes, that is correct.  23 Q (BY MR. ZELLERS) Would you agree that only  24 two of the ten studies in Figure 2 demonstrate  25 statistical significance?</p>	<p style="text-align: right;">Page 169</p> <p>1 A So the way you're asking the question  2 suggests that when you're combining studies in a  3 systematic review, you care about the initial sample  4 size of the question.  5 And so I conclude taken as a group of  6 studies, the individual sample size or power of the  7 individual associations is not sufficient to come up  8 with a narrow confidence interval.  9 And the width of the confidence interval  10 suggests that while the point estimate is greater  11 than one, the confidence interval overlaps one,  12 meaning you can't be sure if it's significantly  13 significant.  14 But the purpose of the systematic review  15 is to combine those studies together. So combining  16 them together gives a very powerful, positive  17 estimate that's very different than one.  18 Q Okay.  19 MR. ZELLERS: Move to strike as  20 nonresponsive.  21 Q (BY MR. ZELLERS) My question is: When you  22 looked at the ten studies together, you determined  23 that there was statistical significance; is that  24 right?  25 A Yes.</p>

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<p>1 Q How did you make that calculation? How</p> <p>2 did you calculate statistical significance from</p> <p>3 those ten studies?</p> <p>4 MS. O'DELL: Object to the form. I</p> <p>5 believe she has already answered that, but you may</p> <p>6 describe that again, Doctor.</p> <p>7 A So the software that was used, is that</p> <p>8 what you are asking?</p> <p>9 Q (BY MR. ZELLERS) I want to know how it is</p> <p>10 that you calculated that these ten studies -- eight</p> <p>11 of which did not demonstrate statistical</p> <p>12 significance when they were looked at together --</p> <p>13 were statistically significant?</p> <p>14 A So I need to provide you with just a</p> <p>15 little background on the field of systematic reviews</p> <p>16 to answer that question.</p> <p>17 Q All right. Well, try to be as direct as</p> <p>18 you can, because I have only got a certain amount of</p> <p>19 time.</p> <p>20 Are you able to answer the question?</p> <p>21 A Absolutely.</p> <p>22 Q Then please tell us how you calculated</p> <p>23 statistical significance for the RE model.</p> <p>24 A So we looked at adjusted odds ratios of</p> <p>25 each of the studies. We weighted them based on the</p>	<p>1 interval around the odds ratio for each of these ten</p> <p>2 studies?</p> <p>3 MS. O'DELL: Object to the form.</p> <p>4 A So most of the studies, if not all of</p> <p>5 those, would have had published adjusted odds ratios</p> <p>6 in the original calculations.</p> <p>7 I believe one of the studies, the Gertig,</p> <p>8 was an adjusted risk ratio, not an odds ratio, which</p> <p>9 had a bit of back-and-forth discussion with the</p> <p>10 biostatistician.</p> <p>11 And we decided they were essentially</p> <p>12 equivalent. But the other ones would have been</p> <p>13 extracted from the initial studies.</p> <p>14 Q The confidence intervals for the ten</p> <p>15 studies on -- in Figure 2, page 33 of your report</p> <p>16 came from the studies themselves?</p> <p>17 A Yes.</p> <p>18 Q Were there any other selection criteria</p> <p>19 that you used to identify these ten studies, other</p> <p>20 than what you have testified to?</p> <p>21 A No.</p> <p>22 Q Of the 43 or so studies that had primary</p> <p>23 data, are these the only studies, other than Terry,</p> <p>24 that discuss regular use of talc?</p> <p>25 A So I am just looking for where my fullest</p>
Page 171	Page 173
<p>1 standard errors for each of them and calculated sort</p> <p>2 of an overlying association when basically the size</p> <p>3 of each study, the point estimate of each study were</p> <p>4 taken into consideration.</p> <p>5 So taking them altogether, it allows the</p> <p>6 summary estimate, if you look, to have a much</p> <p>7 narrower confidence interval than the individual</p> <p>8 study.</p> <p>9 So you use the weight of all the studies</p> <p>10 to combine the -- to give you a summary estimate.</p> <p>11 Q Where can I see the weighting and the</p> <p>12 calculation that you did to come up with the</p> <p>13 statistically significant number?</p> <p>14 A So the -- the name of the software we used</p> <p>15 was in Metafor package in R. "R" is a program.</p> <p>16 The data set that I provided to you of the</p> <p>17 extracted database, if you put those numbers -- if</p> <p>18 anyone puts those numbers in the Metafor package in</p> <p>19 R and instructs the software that you want to apply</p> <p>20 a -- linear mixed models to study that data set, you</p> <p>21 will get the exact same estimate that I got.</p> <p>22 Q And I will be able to see that from the</p> <p>23 documents that you have produced; is that right?</p> <p>24 A Absolutely.</p> <p>25 Q How did you calculate the confidence</p>	<p>1 of studies is in the report. I think it's pages 23</p> <p>2 and 24.</p> <p>3 The fullest of studies that I looked at</p> <p>4 included -- I think there were seven systematic</p> <p>5 reviews. So the systematic reviews did not</p> <p>6 contribute to the -- they were not eligible for --</p> <p>7 for -- for my own review because they didn't have</p> <p>8 primary data, and they would overlap.</p> <p>9 And the same thing with -- well, the</p> <p>10 Terry, we know about. So it was only the other</p> <p>11 studies that were eligible.</p> <p>12 Q These ten studies that you list in</p> <p>13 Figure 2 are the only studies that you reviewed that</p> <p>14 discuss regular use of talc, and that's why you</p> <p>15 included them here; is that right?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A No, that's -- that's not what I said.</p> <p>18 The systematic reviews I read and had</p> <p>19 data, many of them, on regular use of talc.</p> <p>20 But those were not included in my</p> <p>21 systematic review because that would have had</p> <p>22 overlap of -- of -- of patients. So they were not</p> <p>23 included because it overlapped patients.</p> <p>24 Q (BY MR. ZELLERS) Which studies were those</p> <p>25 seven?</p>

<p style="text-align: right;">Page 174</p> <p>1 A So they're listed on page 23 as systematic 2 reviews. So Penninkilampi and Berge and the IARC 3 and Langseth and Huncharek and Gross and Harlow. 4 The reason Terry was pulled out from that 5 to possibly include was because Terry provided new 6 data points that weren't included in the component 7 studies, and so I wanted to make sure not to miss 8 those patients. 9 But these other systematic reviews were 10 all covered in the other primary studies that I 11 included. 12 Q Why did you not include the Cramer study, 13 1999? 14 A Cramer was one of the authors that had a 15 lot of patients that kept appearing in subsequent 16 publications. So he published the same patients 17 more than once, so -- 18 Q What analysis did you do to determine that 19 there was overlap between any of the patients 20 reported on by Cramer in 1999 and any of the ten 21 studies that you did choose to include? 22 A I went through -- I think there's a 23 separate page in my data fields that's just 24 attributed to the Cramer studies -- and wrote down 25 what years of enrollment the patients were.</p>	<p style="text-align: right;">Page 176</p> <p>1 Q (BY MR. ZELLERS) If you turn to -- 2 MS. O'DELL: I'll take that. 3 Q (BY MR. ZELLERS) -- turn to Table 2 on 4 page 353, the bottom table -- at the bottom of the 5 table. 6 A Yes. 7 Q Do you see data with respect to "frequency 8 of use per month"? 9 A Yes. 10 Q That's the type of study and the type of 11 information that you did include in your systematic 12 review; is that right? 13 A Yes. 14 Q Is it fair to say that as you sit here 15 today, you just don't remember why you did not 16 include Cramer 1999? 17 MS. O'DELL: Object to the form. 18 A In looking at this, you have convinced me 19 it's not because he doesn't have frequency of use, 20 because there is frequency of use in here. I do not 21 know why it didn't make it into the final database. 22 But I'm looking at my paper from Cramer 23 from 2016, "The Association Between Talc Use and 24 Ovarian Cancer, a Retrospective Case-control Study." 25 He describes -- this is on page 334 of</p>
<p style="text-align: right;">Page 175</p> <p>1 And to the best I could, I identified the 2 cohorts and then pulled them out to only identify 3 all patients once, which -- which is the reason I 4 hesitated to say there was no overlap. 5 But I did my best to only include every 6 patient once. And -- 7 Q Okay. 8 A -- Cramer got his own worksheet because it 9 was trickier to figure out. 10 Q Cramer 1999 you did not include in your 11 systematic review because you analyzed that paper 12 and the other studies and determined that there was 13 overlap; is that right? 14 A I didn't quite say that. I'm saying that 15 I was very careful not to include overlap patients. 16 I don't know why Cramer 1999 didn't make it into the 17 review. 18 Q I -- 19 A I don't know if he didn't have regular use 20 of talc or -- I -- I -- you know, I would have to -- 21 to figure out why it wasn't included. 22 Q Well, take a look at the Cramer 1999 23 paper, which we'll mark as Exhibit 22. 24 (Exhibit 22 was marked for identification 25 and is attached to the transcript.)</p>	<p style="text-align: right;">Page 177</p> <p>1 that other article -- that data came from three 2 enrollment phases. 3 And my notes on the side say "minus Cramer 4 '99," suggesting -- I don't mind showing you my 5 notes -- showing that there's overlap with Cramer 6 '99 -- 7 Q Okay. 8 A -- so. 9 Q You -- do you believe that the reason you 10 did not include Cramer 1999 is because there was 11 overlap with the patients included in Cramer 2016 or 12 you're not sure? 13 A Yes. 14 MS. O'DELL: Object to the form. 15 Q (BY MR. ZELLERS) Which one is it? 16 MS. O'DELL: Object to the form. 17 A I -- I do not know why it wasn't included, 18 but I believe there was overlap with 2016, is why it 19 was not included. 20 Q (BY MR. ZELLERS) You also did not include 21 Rosenblatt 2011 in your systematic review; is that 22 right? 23 A Rosenblatt was included in the review. 24 But on much -- it looks like it didn't make it into 25 the final graph or the final group of ten.</p>

<p style="text-align: right;">Page 178</p> <p>1 Q Why did it not make it into the final 2 graph or group of ten? 3 A So I don't -- let me just say I don't 4 remember why Rosenblatt was not included. 5 I specifically asked the biostatistician 6 to do the analysis with and without Rosenblatt, and 7 I believe the reason was -- I believe is that -- the 8 quality of Rosenblatt seems very poor, and I can't 9 remember why. 10 But I asked her to do the analysis with 11 and without Rosenblatt. I asked her to do, I think, 12 four different analyses with and without Terry, with 13 and without Rosenblatt. 14 My recollection is it had no impact. But 15 I do not remember why I asked her with the quality 16 issue -- I would have to go back to my database to 17 remember why I asked her to do it both ways. 18 Q Rosenblatt contained information over -- 19 or strike that -- including a lifetime number of 20 applications and included information on more than 21 10,000 lifetime applications, correct? 22 A Yes. 23 Q All right. 24 A Well, I -- I'm -- I'm looking for it. 25 Yeah, I'm guessing that --</p>	<p style="text-align: right;">Page 180</p> <p>1 Q -- the difference in result? 2 A It -- it had no impact on the overall -- 3 Q Was -- 4 A -- results. 5 Q -- it exactly the same? 6 A It was within a decimal fraction of a 7 percent the same. 8 Q Can you tell us what the result was with 9 Rosenblatt included? 10 A It was the same with and without 11 Rosenblatt included -- 12 Q Is -- 13 A -- within a hundredth of a percent. 14 Q Did you produce that calculation for us? 15 A Within the files that I shared, it is 16 included in the forest plot tables that Dr. Hall 17 generated. 18 Q Go to Figure 2, if you will, in your 19 report, page 33. Do you have that? 20 MS. O'DELL: If you need to see the -- the 21 data that you produced, Doctor, the Excel 22 spreadsheets -- 23 A Oh, that would be great. 24 MS. O'DELL: -- okay. And I -- I'm going 25 to hand you my computer. But it's --</p>
<p style="text-align: right;">Page 179</p> <p>1 Q Here is a -- 2 MS. O'DELL: Don't -- don't. Excuse me -- 3 yeah, don't guess. Just if you know. 4 A -- I -- 5 Q (BY MR. ZELLERS) Exhibit 23 is Rosenblatt. 6 A I have got the paper. 7 MS. O'DELL: Yeah. Feel free to take a 8 moment. And if you need your original spreadsheets 9 to answer any of these detailed questions, then we 10 can pull those out for you -- 11 A Okay. 12 MS. O'DELL: -- if counsel does not have a 13 copy for you. 14 Q (BY MR. ZELLERS) Just for the record, 15 Exhibit 23 is Rosenblatt. 16 (Exhibit 23 was marked for identification 17 and is attached to the transcript.) 18 Q (BY MR. ZELLERS) As you sit here, do you 19 know what the difference in results were if 20 Rosenblatt was included in your systematic review or 21 not? 22 A I -- I do. 23 MS. O'DELL: Object to the form. 24 Q (BY MR. ZELLERS) Okay. What is -- 25 A I do.</p>	<p style="text-align: right;">Page 181</p> <p>1 A Can I -- 2 MS. O'DELL: -- it's the data -- 3 A -- this is what I shared with you. 4 MS. O'DELL: -- and that's what she is 5 discussing. 6 Q (BY MR. ZELLERS) Yeah. I have a question 7 pending. If you can answer my -- if you need to 8 look at your counsel's computer to answer my 9 question, you can. 10 But my question is: Will you look at 11 Figure 2 on page 33 of your report. 12 MS. O'DELL: Just hang on. Just -- what 13 I'm showing the doctor is data that -- the tables 14 that she has been discussing, but you have not 15 provided to her, which would be the fair way to 16 examine here on them. 17 But this is the -- the information that 18 was produced to Defendants for purposes of 19 Dr. Smith-Bindman's, you know, deposition. So if 20 you need that, just -- you may refer to it. 21 Q (BY MR. ZELLERS) Are you ready, 22 Dr. Smith-Bindman? 23 A I'm close to ready, but not quite. 24 Q I -- I'm not sure what you are doing. 25 MS. O'DELL: Well, she is looking at the</p>

<p style="text-align: right;">Page 182</p> <p>1 calculation that you were just asking her about.</p> <p>2 Q (BY MR. ZELLERS) I have finished those</p> <p>3 questions. She has answered those questions. I'm</p> <p>4 asking a new question. Or I would like to.</p> <p>5 A Okay. Thank you.</p> <p>6 MS. O'DELL: You're welcome. If you need</p> <p>7 to see any of the tables --</p> <p>8 A Okay.</p> <p>9 MS. O'DELL: -- Doctor, I have all that</p> <p>10 has been produced right here.</p> <p>11 A Fantastic.</p> <p>12 Q (BY MR. ZELLERS) Okay.</p> <p>13 Dr. Smith-Bindman -- Bindman, looking at Figure 2,</p> <p>14 looking at the confidence intervals that you have</p> <p>15 listed for each of those ten studies, are you aware</p> <p>16 that not one of those confidence intervals for any</p> <p>17 of the ten studies are actually listed in or come</p> <p>18 from the study publications?</p> <p>19 MS. O'DELL: Object to the form.</p> <p>20 A I am not aware of that.</p> <p>21 Q (BY MR. ZELLERS) In fact, did you</p> <p>22 recalculate the confidence interval for each of</p> <p>23 these studies?</p> <p>24 A The confidence intervals and the point</p> <p>25 estimate are adjusted confidence intervals and odds</p>	<p style="text-align: right;">Page 184</p> <p>1 (Exhibit 24 was marked for identification</p> <p>2 and is attached to the transcript.)</p> <p>3 Q (BY MR. ZELLERS) Is this another e-mail</p> <p>4 exchange between you and Dr. Hall? Is that yes?</p> <p>5 A I'm so sorry. I didn't hear your</p> <p>6 question.</p> <p>7 Q Sure. My question is: Is this an e-mail</p> <p>8 exchange between you and Dr. Hall?</p> <p>9 A Yes.</p> <p>10 Q If you look at the e-mail at the bottom of</p> <p>11 the second-to-last page, Dr. Hall writes you on</p> <p>12 Monday, September 24, 2018, at 11:42, and tells you</p> <p>13 that she is encountering obstacles; is that right?</p> <p>14 And I'm sorry. It's the third-to-last</p> <p>15 page is where that e-mail starts.</p> <p>16 A I see what you are saying. She has a note</p> <p>17 at the bottom of the page.</p> <p>18 Q She tells you she's encountering</p> <p>19 obstacles?</p> <p>20 A Yes.</p> <p>21 Q She asks you a number of questions?</p> <p>22 A Yes.</p> <p>23 Q No. 1 is that there's missing proportion</p> <p>24 information and the data is missing.</p> <p>25 If you go down to 1B, she says, Where the</p>
<p style="text-align: right;">Page 183</p> <p>1 ratios, so you -- you can't recalculate them from</p> <p>2 the data in the paper.</p> <p>3 Q My -- my question is: Who calculated</p> <p>4 these confidence intervals that appear in Figure 2?</p> <p>5 Did you calculate those confidence intervals?</p> <p>6 A To the best of my knowledge, these</p> <p>7 confidence intervals came from the primary</p> <p>8 publications.</p> <p>9 Q And -- and I will represent to you that I</p> <p>10 have looked at all of the primary publications and</p> <p>11 the confidence intervals that you have listed in</p> <p>12 Figure 2. None of those confidence intervals come</p> <p>13 from the publication.</p> <p>14 So do you have any idea as to how these</p> <p>15 confidence intervals were calculated?</p> <p>16 MS. O'DELL: If there's --</p> <p>17 A You would have to show me --</p> <p>18 MS. O'DELL: Yes.</p> <p>19 A -- those -- those disagreements for me to</p> <p>20 --</p> <p>21 Q (BY MR. ZELLERS) Well, let's --</p> <p>22 A -- to know what we're looking at.</p> <p>23 Q -- let's -- I'll get to that in just a</p> <p>24 second. Let me show you a couple of documents.</p> <p>25 Deposition Exhibit 24.</p>	<p style="text-align: right;">Page 185</p> <p>1 raw numbers are not available, I would do my best to</p> <p>2 estimate unless you have access to them and can send</p> <p>3 them to me.</p> <p>4 How did you respond to that question?</p> <p>5 A Can't we see what my answers were?</p> <p>6 Q Sure. Where are your answers? If you, in</p> <p>7 any of the documents that have been produced, can</p> <p>8 show us how you answered these questions, that would</p> <p>9 be helpful.</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A I would like to just clarify something in</p> <p>12 her request, which is she is not asking me in this</p> <p>13 case for an estimate of the odds ratios or the</p> <p>14 confidence intervals, even although though it seems</p> <p>15 like she is.</p> <p>16 What she is asking for is an estimate of</p> <p>17 the sample size in terms of the N of cases and N of</p> <p>18 controls that can be used for weighting those</p> <p>19 studies in generating the summary estimate.</p> <p>20 So that's where she's trying to fill in</p> <p>21 the blanks, not for the odds ratios or confidence</p> <p>22 intervals, but to calculate -- calculate --</p> <p>23 calculate how -- how much weight it should be in the</p> <p>24 summary statistic.</p> <p>25 Q (BY MR. ZELLERS) How did you respond to</p>



<p style="text-align: right;">Page 186</p> <p>1 her first question where she advised you that there  2 was missing proportion information and her proposal  3 that "where the raw numbers are not available, I'll  4 do my best to estimate, unless you have access to  5 them and can send them to me"?</p> <p>6 MS. O'DELL: Object to the form; asked and  7 answered.</p> <p>8 A I did not have, other than going to the  9 papers, any additional information to supplement.</p> <p>10 Q (BY MR. ZELLERS) Okay. No. 2 --</p> <p>11 MS. O'DELL: Are you finished, Doctor?</p> <p>12 A Say it again.</p> <p>13 MS. O'DELL: Are you finished?</p> <p>14 A No.</p> <p>15 MS. O'DELL: Okay.</p> <p>16 A And so, again, she's not asking me about  17 the abstraction. She's asking me if a study  18 reported, for example, that there were a hundred  19 patients with serous carcinoma or if there were  20 150 patients altogether, it reported the odds ratios  21 for serous carcinoma, but may not have specified in  22 the table how many cases of serous carcinoma there  23 were, could she estimate that proportion when we had  24 the point estimate we needed.</p> <p>25 We had the odds ratio we needed, but she</p>	<p style="text-align: right;">Page 188</p> <p>1 MS. O'DELL: Object to the form.</p> <p>2 A We discussed this at length, and she ended  3 up going with Option 3, using relative risk as an  4 underestimation of the odds ratios, but  5 approximately equal because of the rareness of the  6 disease.</p> <p>7 Q (BY MR. ZELLERS) So she adopted, at your  8 suggestion, the option that she states,  9 understanding that relative risk may considerably  10 underestimate odds ratios; is that right?</p> <p>11 A Yes, it is.</p> <p>12 Q And you advised her -- for No. 3, how did  13 you advise her when she told you that she was unable  14 to calculate the true -- or truly estimate for any  15 talc use and suggested that you consider pooling the  16 results from rarely, monthly, weekly, and daily?</p> <p>17 MS. O'DELL: Object to the form. Are you  18 talking about No. 3? It's not clear.</p> <p>19 A So the option that we did for that choice  20 is actually neither Option 1 or Option 2.</p> <p>21 The focus of the review that she completed  22 was, in fact, on daily talc use. It's not different  23 than she suggested.</p> <p>24 But she used the numbers that were  25 incorrectly categorized as any talc use instead to</p>
<p style="text-align: right;">Page 187</p> <p>1 needed to know how many serous cancers there were to  2 weight it.</p> <p>3 And I would have told her, when the raw  4 numbers for those missing proportions were not  5 available, to do her best to estimate those.</p> <p>6 Q (BY MR. ZELLERS) Did you respond to this  7 e-mail?</p> <p>8 A I sent you all of the documents that I had  9 for our correspondence.</p> <p>10 Q Okay.</p> <p>11 A I certainly could look again to see if I  12 have an answer to this. Or it could be that we  13 discussed the answers on the telephone.</p> <p>14 Q No. 2 --</p> <p>15 A Let me just see if we have -- if it says.  16 I think we spoke on the telephone.</p> <p>17 Q Do you have any notes of that telephone  18 conversation?</p> <p>19 A No, I don't.</p> <p>20 Q All right. No. 2, when she told you that  21 she was unable to calculate the associated  22 95 percent confidence intervals without the  23 variants, which is not reported and she gave you  24 three options, which option did you tell her to  25 follow, if any?</p>	<p style="text-align: right;">Page 189</p> <p>1 represent daily talc use, so that -- that data point  2 was moved for the daily talc use category.</p> <p>3 Q Let me show you the Chang paper. This is  4 one of the papers that you cite both in Figure 2 and  5 again on Figure 3; is that right?</p> <p>6 A Yes.</p> <p>7 Q All right. Here's the Chang paper which  8 we have marked as Exhibit 25.</p> <p>9 A Oh.</p> <p>10 (Exhibit 25 was marked for identification  11 and is attached to the transcript.)</p> <p>12 Q (BY MR. ZELLERS) Do you have that in front  13 of you?</p> <p>14 A I do.</p> <p>15 Q Okay. Show us -- you see in Figure 2,  16 that Chang is listed twice, and it has a confidence  17 interval of .51 to 1.39.</p> <p>18 Do you see that?</p> <p>19 A You said it's listed twice?</p> <p>20 Q I'm sorry. It was -- it's listed in  21 Figure 2 and then you list it again in Figure 3; is  22 that right?</p> <p>23 A Yes.</p> <p>24 Q All right. The first question is: Where  25 in the Chang publication do you get a confidence</p>



<p style="text-align: right;">Page 190</p> <p>1 interval of .51 to 1.39?</p> <p>2 A Hum? So the point estimate that I</p> <p>3 think -- I need to look at the paper a little more</p> <p>4 closely.</p> <p>5 So the number I see in this paper is</p> <p>6 instead of being .51 to 1.39 is .61 to 1.49 is about</p> <p>7 ten points higher.</p> <p>8 Q All right. You don't know where, for</p> <p>9 Figure 2, the confidence interval of .51 to 1.39</p> <p>10 came from, correct?</p> <p>11 A I -- I do not. It's so close to the</p> <p>12 publication -- the publication that I'm not sure if</p> <p>13 it reflects a data abstraction error or if it was --</p> <p>14 I think that's probably what it -- what it does, but</p> <p>15 I'm not sure.</p> <p>16 Q The Chang paper involved 450 patients with</p> <p>17 borderline and invasive ovarian carcinoma; is that</p> <p>18 right?</p> <p>19 A Say it one more time for me.</p> <p>20 Q Sure. The Chang paper --</p> <p>21 A Yeah.</p> <p>22 Q -- Exhibit 25, involved a total of</p> <p>23 450 patients with borderline and invasive ovarian</p> <p>24 carcinoma; is that right?</p> <p>25 A Yes.</p>	<p style="text-align: right;">Page 192</p> <p>1 notes here, but I believe what I did for Chang is</p> <p>2 that Chang's numbers are included in the Terry</p> <p>3 report where she used the data that were published,</p> <p>4 as well as the supplemental data that were provided</p> <p>5 by Chang.</p> <p>6 And within the supplemental data, Terry</p> <p>7 did a stratified analysis that provided additional</p> <p>8 information on serous cancer that was not actually</p> <p>9 in the original Chang report.</p> <p>10 And those are the data that made it into</p> <p>11 what is under Chang in this systematic review.</p> <p>12 Q (BY MR. ZELLERS) Okay.</p> <p>13 A So they're data from Chang's work and</p> <p>14 following Chang's methods. They happen not to be</p> <p>15 published in Chang's original report, but rather</p> <p>16 included in the Terry report from -- from 2013.</p> <p>17 And Terry -- the paper that I am talking</p> <p>18 about for Terry is genital powder use and risk of</p> <p>19 ovarian cancer, a pooled analysis of 8,500 cases and</p> <p>20 ninety-eight hundred fifty-nine controls.</p> <p>21 And then within that describes within the</p> <p>22 methods, getting extra data for studies describing</p> <p>23 the regular use and then breaking down the results</p> <p>24 into whether or not it was invasive borderline,</p> <p>25 invasive serous, and so forth --</p>
<p style="text-align: right;">Page 191</p> <p>1 Q You used or Dr. Hall used, in your</p> <p>2 analysis, only 41 of those 450 patients because</p> <p>3 those are the only ones that had greater than</p> <p>4 25 times of use per month, correct?</p> <p>5 A So I would need to look at my datasheet to</p> <p>6 know how many made it into the analysis, but I</p> <p>7 believe you're correct, that there were</p> <p>8 approximately 10 percent that were frequent users.</p> <p>9 Q How did you determine, just looking at the</p> <p>10 Chang paper, how many of those 41 had invasive</p> <p>11 serous ovarian cancer?</p> <p>12 MS. O'DELL: If you need to look at your</p> <p>13 datasheets --</p> <p>14 A Please.</p> <p>15 MS. O'DELL: Which --</p> <p>16 A That would be great.</p> <p>17 MS. O'DELL: -- which data -- tell -- data</p> <p>18 summary, is that what --</p> <p>19 A Yeah --</p> <p>20 MS. O'DELL: -- you are --</p> <p>21 A -- that should be it.</p> <p>22 MS. O'DELL: Okay. This is both --</p> <p>23 both -- both of the spreadsheets are there, so just</p> <p>24 --</p> <p>25 A Okay. So I don't have all of my detailed</p>	<p style="text-align: right;">Page 193</p> <p>1 Q So --</p> <p>2 A -- so that's where those numbers came</p> <p>3 from.</p> <p>4 Q You believe that if I looked at the Terry</p> <p>5 paper, I would be able to tell of these 41 cases</p> <p>6 that have greater than 25 uses per month, which of</p> <p>7 those cases involved invasive serous ovarian cancer,</p> <p>8 correct?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A I believe the -- I believe the number of</p> <p>11 cases is specified in the Terry paper that I would</p> <p>12 have to look at to find that -- that number.</p> <p>13 Q (BY MR. ZELLERS) All right. Let me ask</p> <p>14 you a few questions.</p> <p>15 A Yes.</p> <p>16 Q In the Chang paper --</p> <p>17 A Yes.</p> <p>18 Q -- the authors do not define "regular use"</p> <p>19 as daily, do they?</p> <p>20 A What Chang says in the original</p> <p>21 publication is questions about regular talc use and</p> <p>22 type of talc use, as well as duration and frequency</p> <p>23 could be derived or included; dusting or powdering</p> <p>24 behavior considered improved regular application of</p> <p>25 talc to the perineum after showering or bathing and</p>

<p style="text-align: right;">Page 194</p> <p>1 dusting.</p> <p>2 And then that was categorized, I believe</p> <p>3 by Terry, as regular use when she got supplemental</p> <p>4 data.</p> <p>5 Q Okay. In the Chang paper, the authors do</p> <p>6 not define "regular use" as daily use, correct?</p> <p>7 MS. O'DELL: Object to the form; asked and</p> <p>8 answered.</p> <p>9 A The Chang paper explicitly says "regular</p> <p>10 use." In the original publication, they don't</p> <p>11 define it.</p> <p>12 Q (BY MR. ZELLERS) They do not include</p> <p>13 information in the Chang paper about how many times</p> <p>14 per week women used talcum powder, correct?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A In -- in Table 2 of Chang, they define it</p> <p>17 as less than ten, ten to 25, or greater than 25</p> <p>18 times per week.</p> <p>19 Q (BY MR. ZELLERS) Where do you see that?</p> <p>20 A In Chang?</p> <p>21 Q Yes. I'm looking at the same table, and I</p> <p>22 think it's per month.</p> <p>23 A Per month.</p> <p>24 Q Okay. And that's the only data that's</p> <p>25 provided with respect to use is the number of</p>	<p style="text-align: right;">Page 196</p> <p>1 of invasive besides just serous.</p> <p>2 Q Do you know that?</p> <p>3 A I -- I don't think they specify what's</p> <p>4 included in that. I have to add up the total to see</p> <p>5 if they are overlapping or not overlapping.</p> <p>6 Could you add -- could you add that for</p> <p>7 me? Actually, the total should be -- they're</p> <p>8 overlapping. 360, 460. Yeah, they're overlapping.</p> <p>9 Yeah.</p> <p>10 Q What do you mean, "they're overlapping"?</p> <p>11 A Invasive and borderline should add up to</p> <p>12 the total.</p> <p>13 And then serous mucin -- mucinous and</p> <p>14 endometrioid should add up to the total, except to</p> <p>15 the degree that they are missing information.</p> <p>16 Q Looking at the questions that Dr. Hall</p> <p>17 asked you --</p> <p>18 A Yes.</p> <p>19 Q -- in Exhibit 24, you would agree that</p> <p>20 there were number of assumptions that you and she</p> <p>21 made in order to complete your systematic review; is</p> <p>22 that right?</p> <p>23 A Absolutely.</p> <p>24 Q Is there anywhere that you have written</p> <p>25 down, you know, what the assumptions were that you</p>
<p style="text-align: right;">Page 195</p> <p>1 monthly applications, correct?</p> <p>2 A Yes.</p> <p>3 Q The authors of Chang did not arrive at a</p> <p>4 specific odds ratio for serous invasive cancer based</p> <p>5 on frequency of use, correct?</p> <p>6 A The Chang data was used by Terry to</p> <p>7 calculate frequency of use for serous and invasive</p> <p>8 by supplementing the original data that they had</p> <p>9 from additional data from Chang as a participant in</p> <p>10 the OCAC consortium.</p> <p>11 So additional data from that study was</p> <p>12 shared with Terry, which is what we used in our</p> <p>13 analysis.</p> <p>14 Q If we look at Chang in Table 3, they</p> <p>15 describe a histologic type of invasive; is that</p> <p>16 right, in Table 3, page 2399?</p> <p>17 A Yes.</p> <p>18 Q They also describe serous; is that right?</p> <p>19 A Yes.</p> <p>20 Q In the Chang data, what's the difference</p> <p>21 between invasive and serous?</p> <p>22 A I'm -- I'm sorry. In lot -- in Table 3</p> <p>23 you're asking what those different entries mean?</p> <p>24 Q Yes.</p> <p>25 A "Invasive" presumably includes other types</p>	<p style="text-align: right;">Page 197</p> <p>1 and Dr. Hall arrived at, at least in part in</p> <p>2 response to her questions?</p> <p>3 A So for some of the issues, it took me</p> <p>4 quite a bit of remembering to remember that we used</p> <p>5 some of the extracted data from more than one</p> <p>6 source.</p> <p>7 We have notes in our data form of what the</p> <p>8 source of the data was, so it would say in some of</p> <p>9 the data I said -- under Chang, it would say "in a</p> <p>10 column from Terry."</p> <p>11 Q My question --</p> <p>12 A So that -- that -- so to answer the</p> <p>13 assumption of where the data came from, it's in my</p> <p>14 data spreadsheet. I just -- I just didn't remember</p> <p>15 that we pulled data.</p> <p>16 Q My -- my question is a little different I</p> <p>17 --</p> <p>18 A Okay.</p> <p>19 Q -- think. In terms of all of the</p> <p>20 questions that Dr. Hall asked you and all of the</p> <p>21 assumptions that would need to be made so that</p> <p>22 estimates could be arrived at, do you have either</p> <p>23 your protocol or a listing of the assumptions that</p> <p>24 were made by you and by Dr. Hall in -- at least in</p> <p>25 part in response to the question she raised?</p>

<p style="text-align: right;">Page 198</p> <p>1 MS. O'DELL: Objection, asked and                  2 answered. Respond.                  3 A I am under the impression that they're                  4 documented within our e-mail exchanges, but I do not                  5 have a protocol with each of these decisions that                  6 are laid out.                  7 Q (BY MR. ZELLERS) I -- my best source would                  8 be the e-mail exchanges that you had with Dr. Hall,                  9 correct?                  10 MS. O'DELL: Object to the form.                  11 Q (BY MR. ZELLERS) Is that right?                  12 A Yes.                  13 Q Okay. Once you did your ten studies that                  14 are in Figure 2 -- and those were just the --                  15 the studies that you chose to include, as you have                  16 told us, showing odds of ovarian cancer associated                  17 with regular use of talcum powder -- you further                  18 refined the studies or narrowed down the studies to                  19 four which you state plot or who the odds of ovarian                  20 cancer associated with regular use of talcum powder                  21 and invasive serous cancer; is that right?                  22 MS. O'DELL: Object to the form.                  23 A With the caveat that when -- when I laid                  24 out our stratified analysis on page 32, it says, My                  25 review focused on invasive serous cancer where</p>	<p style="text-align: right;">Page 200</p> <p>1 confidence interval for the -- let's say the Chang                  2 data that you list in Figure 3?                  3 A I'm going to have to look into the exact                  4 calculation of the confidence interval.                  5 The question that you asked me about Chang                  6 for the first table is very close to the one that's                  7 published -- so close -- that I'm not sure how it                  8 would be different.                  9 I don't -- I thought these were abstracted                  10 from the paper. And I would have to go back and                  11 talk to Dr. Hall about how they were calculated.                  12 I thought they were calculated, but I -- I                  13 may be -- I may be wrong. They may have been in                  14 some way reestimated.                  15 So again, similar with this, these numbers                  16 are close to the ones that are in this paper, but                  17 are slightly off, and I'm not sure why.                  18 So I would have to go back to the data                  19 that I abstracted and then the data that she sent me                  20 back for the final tables to see why they were                  21 different.                  22 Q Okay.                  23 A But they're -- they're different to a --                  24 such a slight degree that -- and I'm not really sure                  25 where that difference came from.</p>
<p style="text-align: right;">Page 199</p> <p>1 possible, but also included all invasive cancer.                  2 Q (BY MR. ZELLERS) What did you do to get                  3 from the ten studies that you list in Figure 2 to                  4 the four studies that you list in Figure 3?                  5 A Figure 2 is ovarian cancer with regular                  6 use, and Figure 3 is invasive serous cancer.                  7 If there was not invasive serous but there                  8 was just invasive, they also might be in this. I                  9 would have to review these four studies to know if                  10 it was invasive or invasive serous.                  11 Q Do you know, as you sit here, what you did                  12 to go from the ten studies in Figure 2 to the four                  13 studies in Figure 3?                  14 MS. O'DELL: Object to the form.                  15 A In the data set that I sent to you and                  16 sent to Dr. Hall, they would -- there were different                  17 sets of complete data. And the Figure 3 had data                  18 for invasive or invasive serous cancer; whereas,                  19 Figure 2 had -- included invasive and noninvasive.                  20 So it would just be where there were data                  21 available in the data worksheet. I -- I was not                  22 involved in making the selection to go from one to                  23 the other. It was just where there were data that                  24 were abstracted from the papers.                  25 Q (BY MR. ZELLERS) Where did you get the</p>	<p style="text-align: right;">Page 201</p> <p>1 Q Were there any other analyses that you or                  2 Dr. Hall con -- conducted that are not included in                  3 your report?                  4 A I had asked Dr. Hall, I believe, to look                  5 at -- at several analyses that are all in the data                  6 that I shared with you.                  7 The sensitivity analysis for Terry and the                  8 sensitivity analysis for the Rosen [sic] study are                  9 in the data I sent you, but are not summarized in                  10 the report.                  11 MS. O'DELL: And by "the data," you're                  12 talking about the spreadsheets --                  13 A Yes.                  14 MS. O'DELL: -- that you provided?                  15 A Yes. There -- there are more analyses                  16 that were done that you haven't seen. But they --                  17 they were analysis for four analyses.                  18 I just see two here. So I -- there were                  19 two others. I think it was including Terry and                  20 including Rosenblatt, I think, are the other two.                  21 But you have all of the -- there were no                  22 other analyses except those four that she completed.                  23 MS. O'DELL: Excuse me, Mike. I'm sorry.                  24 We're right at 3:00 p.m. When you get to a stopping                  25 point, can we take a break?</p>

<p style="text-align: right;">Page 202</p> <p>1 MR. ZELLERS: All right. Let's stop.  2 We're stopping for the day; is that right?  3 MS. O'DELL: Let's -- let me speak with  4 Dr. Smith-Bindman on the break and then I'll let you  5 know.  6 MR. ZELLERS: All right.  7 THE VIDEOGRAPHER: We're off the record at  8 2:59 p.m.  9 (A break was taken from 2:59 p.m. to  10 3:11 p.m.)  11 THE VIDEOGRAPHER: We are back on the  12 record. This marks the beginning of Disc No. 4 in  13 the deposition of Dr. Rebecca Smith-Bindman. The  14 time is 3:11 p.m.  15 Q (BY MR. ZELLERS) Dr. Smith-Bindman, what  16 methodology, if anything different, did you use to  17 arrive at your opinion that there was a causal  18 association between genital talcum powder use and  19 ovarian cancer?  20 A I used the Bradford Hill criteria.  21 Q Are you familiar with the Bradford Hill  22 criteria?  23 A I am. Yes, I am.  24 Q You're familiar that over time the FDA has  25 gone through and done various analyses with respect</p>	<p style="text-align: right;">Page 204</p> <p>1 Q The FDA, in 2014, reviewed the  2 epidemiology and etiology findings relating to  3 ovarian cancer and the genital application of talc;  4 is that right?  5 MS. O'DELL: Object to the form.  6 A Yes.  7 Q (BY MR. ZELLERS) The FDA noted that  8 selection bias and/or uncontrolled confounding  9 result in spurious positive associations between  10 talc use and ovarian cancer; is that right?  11 MS. O'DELL: Object to the form.  12 A The FDA concluded that some of the studies  13 had biases. Yes, they did.  14 Q (BY MR. ZELLERS) And if we look at No. 2,  15 the FDA states, No single study has considered all  16 the factors that potentially contribute to ovarian  17 cancer, including selection biased and/or  18 uncontrolled confounding that result in spurious  19 positive associations between talc use and ovarian  20 cancer risk.  21 Is that right?  22 A That is what the FDA concluded.  23 Q The FDA also noted that there was a lack  24 of consistency in the study results; is that right?  25 A That is what the FDA concluded.</p>
<p style="text-align: right;">Page 203</p> <p>1 to perineal talcum powder use and any association  2 with ovarian cancer; is that right?  3 MS. O'DELL: Object to the form.  4 A I -- I have seen some documents by the  5 FDA.  6 Q (BY MR. ZELLERS) And the FDA, back in  7 2014, did a review and analysis of the epidemiology  8 at that time; is that right?  9 MS. O'DELL: Object to the form.  10 A Could you show me that document?  11 Q (BY MR. ZELLERS) Sure. This is a document  12 that we'll mark as Exhibit 26.  13 (Exhibit 26 was marked for identification  14 and is attached to the transcript.)  15 Q (BY MR. ZELLERS) It's a document from the  16 FDA. It's got a date stamp at the top --  17 MS. O'DELL: Thank you.  18 Q (BY MR. ZELLERS) -- April 1 of 2014.  19 Is this one of the documents that you have  20 reviewed in connection with your expert work in this  21 matter?  22 A Yes, it is.  23 Q Turn, if you will, to page 4 of that  24 document. Do you see that?  25 A Yes.</p>	<p style="text-align: right;">Page 205</p> <p>1 Q And specifically the FDA concludes,  2 Results of case-control studies do not demonstrate a  3 consistent, positive association across studies; is  4 that right?  5 MS. O'DELL: I think it says something  6 further than that.  7 A Can I just add something? This -- the FDA  8 did some review that I don't know the details of.  9 And this is their summary of that review, which I  10 don't know the details of, yes.  11 Q (BY MR. ZELLERS) The FDA, at least in this  12 review, stated that dose response evidence is  13 lacking; is that right?  14 And I am looking at the end of Point No. 3  15 on page 4.  16 A That is what the FDA concluded.  17 Q And looking at Point No. 4, the FDA found  18 that a cogent biological mechanism was lacking; is  19 that right?  20 A That is what the FDA concluded.  21 Q You have reviewed IARC; is that right?  22 And I think in your blue folder here you have  23 included some IARC documents?  24 A I have included IARC work reflecting  25 analysis through 2006 and then more recently</p>

<p style="text-align: right;">Page 206</p> <p>1 through -- through 2010, each published a few years</p> <p>2 after that.</p> <p>3 Q IARC has gone through and addressed the</p> <p>4 Bradford Hill considerations with respect to the</p> <p>5 classification of genital talc; is that right?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A Can you remind me which analysis you're</p> <p>8 referring to?</p> <p>9 Q (BY MR. ZELLERS) Well, let's start with</p> <p>10 the classifications. Take a look at Exhibit 27, if</p> <p>11 you will.</p> <p>12 (Exhibit 27 was marked for identification</p> <p>13 and is attached to the transcript.)</p> <p>14 Q (BY MR. ZELLERS) Are these the IARC</p> <p>15 classifications for its determination --</p> <p>16 MS. O'DELL: Thank you.</p> <p>17 Q (BY MR. ZELLERS) -- as to the</p> <p>18 carcinogenicity -- carcinogenicity of different</p> <p>19 agents?</p> <p>20 A Yes.</p> <p>21 Q And you're generally familiar with these</p> <p>22 classifications; is that right?</p> <p>23 A I am.</p> <p>24 Q Group 1, these are the agents that IARC</p> <p>25 has determined are carcinogenic to humans, correct?</p>	<p style="text-align: right;">Page 208</p> <p>1 prove that something is safe is -- is next to</p> <p>2 impossible --</p> <p>3 Q (BY MR. ZELLERS) Right.</p> <p>4 A -- and so that's why that category is</p> <p>5 not -- is used. Category 3 and four can, for the</p> <p>6 sake of discussion, be considered the same.</p> <p>7 Q And that's why there's no Group 5, not</p> <p>8 carcinogenic; is that right?</p> <p>9 A Yes.</p> <p>10 Q Correct? Now, with genital talc, IARC has</p> <p>11 determined that it is appropriately placed in the</p> <p>12 "to be" category; is that right?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A I -- I would take a slight pause to that</p> <p>15 consideration. I think that in the first review</p> <p>16 when they have looked at platy talc, they consider</p> <p>17 it a "to be" possibly carcinogenic to humans.</p> <p>18 Whereas, in the report looking at asbestos</p> <p>19 and fibrous talc, which also counts in the same</p> <p>20 category as asbestos, the -- that is in the category</p> <p>21 that's a Group 1 carcinogenic to humans.</p> <p>22 Q (BY MR. ZELLERS) IARC has determined that</p> <p>23 genital talc is a group to be possibly carcinogenic</p> <p>24 to humans; is that right?</p> <p>25 MS. O'DELL: Object to the form.</p>
<p style="text-align: right;">Page 207</p> <p>1 A Yes.</p> <p>2 Q And that's the only category in which IARC</p> <p>3 finds sufficient evidence in humans; is that right?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A That's how they define that category.</p> <p>6 Q (BY MR. ZELLERS) IARC puts 82 agents in</p> <p>7 Group 2A probably carcinogenic to humans; is that</p> <p>8 right?</p> <p>9 A That is correct.</p> <p>10 Q So IARC has gone through and has evaluated</p> <p>11 many, many, many agents and has determined that</p> <p>12 there are over 200 agents in both the Group 1</p> <p>13 category and also the Group 2A category, correct?</p> <p>14 A Yes.</p> <p>15 Q There's only one agent in Group 4,</p> <p>16 probably not carcinogenic to humans; is that right?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A Yes, that's correct.</p> <p>19 Q (BY MR. ZELLERS) So out of the over a</p> <p>20 thousand agents that IARC has reviewed, it's only</p> <p>21 placed one agent in Group 4 probably not</p> <p>22 carcinogenic; is that right?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A To be considered by IARC, there has to be</p> <p>25 data to suggest there's some potential harm. And to</p>	<p style="text-align: right;">Page 209</p> <p>1 Misstates her testimony.</p> <p>2 A So in their initial review -- in their</p> <p>3 earlier review, they concluded that genital talc is</p> <p>4 possibly carcinogenic to humans.</p> <p>5 In the more recent 2012, they discuss that</p> <p>6 cosmetics are the primary sources of exposure to</p> <p>7 talc in the general population; that perineal</p> <p>8 application is the primary route and that fibrous</p> <p>9 talc, which is part of talc, is actually Group 1</p> <p>10 carcinogenic.</p> <p>11 Q (BY MR. ZELLERS) All right. Show me the</p> <p>12 IARC designation of genital talc as a Group 1</p> <p>13 carcinogenic.</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A Genital talc contains platy talc, as well</p> <p>16 as fibrous talc, as well as asbestiform contaminated</p> <p>17 talc, and they consider any fibrous talc to be a</p> <p>18 Group 1 carcinogen.</p> <p>19 Q (BY MR. ZELLERS) Show me where the</p> <p>20 perineal application of genital talc has been</p> <p>21 determined by IARC to be a Group 1 carcinogen.</p> <p>22 MS. O'DELL: Object to the form. Would</p> <p>23 you like to see the IARC?</p> <p>24 A Can you show me the IARC report?</p> <p>25 Q (BY MR. ZELLERS) No. I would like you --</p>



<p style="text-align: right;">Page 210</p> <p>1 you're the one who is testifying.</p> <p>2 A I just don't have the document in front of</p> <p>3 me. How would you like me to show it to you?</p> <p>4 Q I -- I would like you to show me where</p> <p>5 genital talc has been found by IARC to be a Group 1</p> <p>6 carcinogen.</p> <p>7 MS. O'DELL: Object to the form. So was</p> <p>8 that not -- excuse me, Doctor. Is that not</p> <p>9 something you're going to put in front of her?</p> <p>10 Q (BY MR. ZELLERS) I -- I have my</p> <p>11 information. And my IARC review says that they have</p> <p>12 classified genital talc as a group to be possibly</p> <p>13 carcinogenic to humans.</p> <p>14 A Do you have the 2012 --</p> <p>15 MS. O'DELL: Yes. Let me just get it for</p> <p>16 you, Doctor. Give me a moment to see what number it</p> <p>17 is in your references.</p> <p>18 Q (BY MR. ZELLERS) As your counsel is</p> <p>19 looking for that document, can we agree that the "to</p> <p>20 be" designation with IARC is based on limited</p> <p>21 evidence in humans, which means IARC cannot rule out</p> <p>22 chance, bias, or confounding with reasonable</p> <p>23 confidence?</p> <p>24 A In their original assessment of talc in</p> <p>25 2010 where they classified it as to be, the "to be"</p>	<p style="text-align: right;">Page 212</p> <p>1 A So this is the monograph -- the</p> <p>2 monograph -- the IARC monograph on the evaluation of</p> <p>3 carcinogenic risks -- arsenic metals, fibrous and</p> <p>4 dust, volume 100C. So --</p> <p>5 Q I'm looking for perineal talc.</p> <p>6 A No. No. I know. I understand.</p> <p>7 Q Okay.</p> <p>8 A I'm just telling you where I'm -- I'm</p> <p>9 going to be pulling this from. And I'm looking at</p> <p>10 the section under "Asbestos." And under the Pier --</p> <p>11 the -- the section under "Asbestos, it talks, under</p> <p>12 1.C --</p> <p>13 Q What page?</p> <p>14 A -- 230. And I will read several sections</p> <p>15 of it. This section says, Talc particles are</p> <p>16 normally plate-like. These particles are viewed on</p> <p>17 edge under the microscope.</p> <p>18 THE COURT REPORTER: I have to have you</p> <p>19 slow down when you read.</p> <p>20 A I'm so sorry. May appear to be fibers.</p> <p>21 Talc may also form true mineral fibers that are</p> <p>22 asbestiform in habit.</p> <p>23 In some talc deposits, tremolite,</p> <p>24 anthophyllite, and actinolite may occur. Talc</p> <p>25 containing asbestiform fibers is a term that has</p>
<p style="text-align: right;">Page 211</p> <p>1 designation means that it's possibly carcinogenic,</p> <p>2 which is a very high bar for them to put them in</p> <p>3 that category, but could also be due to chance.</p> <p>4 Q Okay. Also, in class "to be" as possibly</p> <p>5 carcinogenic is ginkgo biloba; is that right?</p> <p>6 A I -- I have no idea.</p> <p>7 Q Occupational carpentry and joinery; is</p> <p>8 that right?</p> <p>9 A I -- I -- I have no idea.</p> <p>10 Q Pickled --</p> <p>11 A I --</p> <p>12 Q -- vegetables?</p> <p>13 A -- I think pickled vegetables are pretty</p> <p>14 carcinogenic, but I -- I don't know what IARC thinks</p> <p>15 of them.</p> <p>16 Q Do you believe that the standard for</p> <p>17 prove -- proving causation in the scientific</p> <p>18 literature is the same as the one that applies in</p> <p>19 litigation?</p> <p>20 A Yes, I do.</p> <p>21 Q Do you want to show me what your counsel</p> <p>22 has provided you?</p> <p>23 A Yes.</p> <p>24 Q And I am looking for the finding that IARC</p> <p>25 that genital talc use is a Group 1 carcinogen.</p>	<p style="text-align: right;">Page 213</p> <p>1 been used inconsistently.</p> <p>2 I'm -- I'm just seeing where the --</p> <p>3 Q (BY MR. ZELLERS) That's okay. And I am</p> <p>4 looking for the statement or the finding that</p> <p>5 genital talc -- cosmetic genital talc has been</p> <p>6 determined by IARC to be a Group 1 carcinogen.</p> <p>7 A So I'm in the section --</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A -- on the talc and asbestiform talc. And</p> <p>10 under 1.65, "Human Exposure," under "A," it says,</p> <p>11 Exposure of the general population: Consumer</p> <p>12 products, cosmetics, pharmaceuticals are the primary</p> <p>13 source of exposure to talc for the general</p> <p>14 population. Inhalation and dermal contact through</p> <p>15 perineal application are the primary routes of</p> <p>16 exposure.</p> <p>17 Q (BY MR. ZELLERS) Where does IARC conclude</p> <p>18 that perineal talc use, cosmetic talc, is a Group 1</p> <p>19 carcinogen?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A As late as 1973, talc products contained</p> <p>22 detectable levels of chrysotile asbestos, tremolite,</p> <p>23 or anthophyllite role. And it's possible they</p> <p>24 remained on the market in some places for some time</p> <p>25 after that. And these are asbestiform in habit.</p>



<p style="text-align: right;">Page 214</p> <p>1 It goes on to cite a whole lot of other                  2 places, Blount and so forth.                  3 And then in this same document they                  4 categorize the asbestos and asbestiform fibers as                  5 being a Group 1 carcinogen.                  6 Q (BY MR. ZELLERS) I'm going to ask you                  7 about asbestos and I'm going to ask you about                  8 asbestiform fibers.                  9 What I want to know is: Where does IARC,                  10 in the publication you're looking at, categorize                  11 cosmetic talc applied perineal -- to the perineal                  12 region as a Group 1 carcinogen?                  13 MS. O'DELL: Object to the form.                  14 A They're telling us in this document that                  15 asbestos and asbestiform talc are Group 1                  16 carcinogens.                  17 They're telling us at the cite -- the --                  18 the most common exposure is consumer products. And                  19 inhalation and dermal contact with perineal                  20 application of talc powders are the primary routes                  21 of exposure.                  22 Q (BY MR. ZELLERS) Where does IARC state                  23 that perineal use of cosmetic talc is a Group 1                  24 carcinogen?                  25 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 216</p> <p>1 MS. O'DELL: As I'm not coaching the                  2 witness. So you can ask the questions, but you                  3 can't raise your voice and -- and continue --                  4 MR. ZELLERS: We have a video record.                  5 MS. O'DELL: -- yes, we do.                  6 MR. ZELLERS: No one here would say that                  7 I'm raising my voice to the witness or behaving in                  8 any way other than professionally.                  9 A I'm looking for the executive summary.                  10 It's just taking a while in this very large document                  11 to -- I see the problem.                  12 The copy of this document, I'm missing my                  13 first few pages.                  14 Q (BY MR. ZELLERS) Okay.                  15 A It starts at 30 -- 31.                  16 THE COURT REPORTER: Did you say "few" or                  17 "first three"?                  18 A I think I'm missing the first 30 pages.                  19 Q (BY MR. ZELLERS) All right. Let --                  20 A So --                  21 Q -- me move on then.                  22 A -- okay.                  23 Q Strength of association is a Bradford Hill                  24 criteria -- is that -- criterion; is that right?                  25 A Yes, it is.</p>
<p style="text-align: right;">Page 215</p> <p>1 A So IARC is telling us which compounds are                  2 Group 1 carcinogens.                  3 Q (BY MR. ZELLERS) Where does it state that                  4 the perineal use of cosmetic talc is a Group 1                  5 carcinogen?                  6 MS. O'DELL: Object to the form. She has                  7 already stated that three times.                  8 MR. ZELLERS: Well, I haven't heard it                  9 yet --                  10 MS. O'DELL: Yes.                  11 MR. ZELLERS: -- Counsel.                  12 MS. O'DELL: Yes, you -- she has described                  13 it to you three times or four times maybe. And so                  14 she has --                  15 MR. ZELLERS: Counsel --                  16 MS. O'DELL: -- answered your question.                  17 MR. ZELLERS: -- please don't coach the                  18 witness. Just --                  19 MS. O'DELL: -- I'm not -- I'm not --                  20 MR. ZELLERS: -- object to form, if you                  21 want to object to form.                  22 MS. O'DELL: -- well, don't harass the                  23 witness, which -- that's what I am --                  24 MR. ZELLERS: I'm not harassing the                  25 witness.</p>	<p style="text-align: right;">Page 217</p> <p>1 Q You -- one of the studies you reviewed was                  2 Langseth; is that right?                  3 A Yes, it is.                  4 Q Langseth reviewed the overall pooled odds                  5 of cancer and found that there was an odds ratio of                  6 1.35 across the studies; is that right?                  7 A I'm going to look for it, but --                  8 Q Okay. I --                  9 A -- it sounds about right.                  10 Q -- I will hand you Langseth.                  11 A I have it.                  12 Q If you take a look at page 359,                  13 Figure 1 -- do you see that -- do you know Langseth?                  14 A I do.                  15 Q Langseth looks at the case-control                  16 studies, both the population-based and the                  17 hospital-based; is that right?                  18 A He looked at the studies that had a -- he                  19 had available when this was established a decade                  20 ago, yes.                  21 Q And -- and he lists out 20 case-control                  22 studies, correct?                  23 A 14?                  24 Q I'm looking at the chart above Figure 1.                  25 And you think there's only 14 studies there?</p>

<p style="text-align: right;">Page 218</p> <p>1 A Oh, I apologize. I thought you were                  2 talking about the population-based studies.                  3 No. You're absolutely right. 20 studies.                  4 Q And of those 20 studies, only ten have                  5 statistical significance; is that right?                  6 A The original studies with the sample size                  7 they had, ten seemed to have difference than one.                  8 Q Of the 20 studies -- the 20 case-control                  9 studies that were available and were studied by                  10 Langseth, only ten had statistically significant                  11 results; is that right?                  12 MS. O'DELL: Object to the form.                  13 A Again, he is combining them together. But                  14 in the original form when they were not combined,                  15 there are ten in their original form that had                  16 statistical differences than one. They could                  17 exclude one.                  18 Q (BY MR. ZELLERS) Half of the studies did                  19 not have statistically significant results; is that                  20 right?                  21 A The original studies had wide confidence                  22 intervals. And the original studies, before they                  23 were combined, many of them overlapped one.                  24 Q Is the answer yes to my question?                  25 MS. O'DELL: She has answered your</p>	<p style="text-align: right;">Page 220</p> <p>1 a causal association between perineal use of talc                  2 and ovarian cancer?                  3 MS. O'DELL: Objection to form.                  4 A The Langseth study is one review. And as                  5 I describe in my report, it seems like a well-done                  6 review, although it does not provide the kind of                  7 details that I would hope it would provide given                  8 sort of the stature of some of the people who were                  9 involved in writing the report.                  10 That being said, this systematic review                  11 suggests that there's an association between                  12 perineal talc exposure and ovarian cancer.                  13 Q You --                  14 A By itself, I don't think it provides                  15 enough data to have causality, but it provides good                  16 evidence that there's an association.                  17 Q You understand that your interpretation of                  18 this study is different and broader than the                  19 authors' interpretation of the data, correct?                  20 MS. O'DELL: Object to the form.                  21 A One of the author's conclusion that I                  22 found quite compelling was in -- on page 358 in the                  23 second paragraph -- in the second column --                  24 Q (BY MR. ZELLERS) Can you answer my                  25 question?</p>
<p style="text-align: right;">Page 219</p> <p>1 question.                  2 MR. ZELLERS: Well, I -- I don't know. I                  3 haven't heard an answer.                  4 MS. O'DELL: You have heard a complete                  5 answer.                  6 A You're asking me to look at the results in                  7 Figure 1 --                  8 Q (BY MR. ZELLERS) Yes.                  9 A -- which are meant to combine results.                  10 But they also had the individual original study                  11 sample size and show that about half of them overlap                  12 one.                  13 Q Half is no better than a coin toss,                  14 correct?                  15 MS. O'DELL: Object to the form.                  16 A It's an interesting question. But if                  17 you're looking for something, is there an                  18 association with an exposure with cancer, a random                  19 selection of that, you would expect to find very few                  20 positive associations.                  21 To find half is an enormous association to                  22 find from random studies if there was no                  23 association.                  24 Q (BY MR. ZELLERS) Do you believe that based                  25 upon the Langseth paper and analysis, that there is</p>	<p style="text-align: right;">Page 221</p> <p>1 MS. O'DELL: She has answered your                  2 question. Don't --                  3 MR. ZELLERS: Well, I don't think she is                  4 answering my question.                  5 A I think you are asking me about what the                  6 authors conclude.                  7 Q (BY MR. ZELLERS) I asked if your                  8 conclusion was broader than the authors' --                  9 MS. O'DELL: And she is telling you what                  10 the authors' conclusions are. You may finish,                  11 Doctor.                  12 A What -- what Langseth says is that, Eight                  13 of the population-based case-control studies were                  14 identified by the Arforthinger (phonetic) as being                  15 the most informative in terms of the size of the                  16 studies, whether the studies were population-based                  17 participation rates and adjustment for confounding                  18 variables. These selected studies -- among these                  19 eight studies, the prevalence of use of talc was 16                  20 to --                  21 THE COURT REPORTER: I can't hear.                  22 A -- sorry. The selected studies included                  23 at least 188 cases and had participation rates                  24 ranging up to 75 percent. Among these eight                  25 studies, the prevalence of peritoneal use of</p>

<p style="text-align: right;">Page 222</p> <p>1 talc-based body powder among controls ranged from 16                  2 to 52 percent.                  3 The relative risk of ovarian cancer among                  4 body powder users were homogeneous across the set of                  5 eight studies, each of which indicated a 30 to                  6 60 percent increase in risk.                  7 Among the other 12 case-control studies,                  8 most also reported relative risk of this magnitude                  9 or higher.                  10 So I think the authors of this concluded                  11 that the better studies showed a very strong                  12 association. And -- and I -- I'm not sure what                  13 conclusion of the authors you're asking me to                  14 disagree with.                  15 Q (BY MR. ZELLERS) Okay. Doctor, take a                  16 look at "Proposal to Research Community" on the                  17 right-hand side of page 359.                  18 Do you see that?                  19 A I do.                  20 Q I'm going to read this, and you tell me if                  21 I read it correctly.                  22 "The current body of experimental and                  23 epidemiological evidence is insufficient to                  24 establish a causal association between perineal use                  25 of talc and ovarian cancer risk.</p>	<p style="text-align: right;">Page 224</p> <p>1 as nonresponsive.                  2 My question was: Did I read that                  3 correctly?                  4 A You read that text correctly.                  5 Q All right. You conclude in your report                  6 with respect to strength of association that because                  7 a very large number of ovarian cancers are caused by                  8 talcum powder and talcum powder provides no                  9 better -- no medical benefit, the Hill criterion of                  10 strength of association is important and met.                  11 Is that right?                  12 A I don't think that's exactly right. I --                  13 I think all of the things I believe are in there                  14 somewhere, but that's not quite what I would be --                  15 Q I --                  16 A -- report.                  17 Q -- I'm just reading from page 38 of your                  18 report. Do you believe that because a very large                  19 number of ovarian cancers are caused by talcum                  20 powder and talcum powder provides no medical                  21 benefit, the Hill criterion of strength of                  22 association is important and is met?                  23 MS. O'DELL: Object to the form. I don't                  24 think you read that --                  25 A I --</p>
<p style="text-align: right;">Page 223</p> <p>1 Experimental research is needed to better                  2 characterize deposition, retention, and clearance of                  3 talc to evaluate the ovarian carcinogenicity of                  4 talc."                  5 Did I read that correctly?                  6 A Not only did you read that correctly, I                  7 would agree with that based on data available in                  8 2008.                  9 So you asked me if I thought this study by                  10 itself evaluated causality.                  11 And this study did not discuss the                  12 deposition, the retention, or clearance. And I                  13 think those factors are crucial to understanding the                  14 causality.                  15 Q Okay.                  16 A And that's new since --                  17 MR. ZELLERS: Move --                  18 A -- 2008.                  19 MR. ZELLERS: -- to strike as not --                  20 MS. O'DELL: She is --                  21 MR. ZELLERS: -- she finished.                  22 MS. O'DELL: -- she did not finish.                  23 MR. ZELLERS: Did you finish?                  24 A I was close enough.                  25 MR. ZELLERS: All right. Move to strike</p>	<p style="text-align: right;">Page 225</p> <p>1 MS. O'DELL: -- the report correctly. But                  2 if you were intending to read from her report                  3 verbatim, I don't believe that was correct.                  4 MR. ZELLERS: Counsel, please, just object                  5 to form, if you do have an objection.                  6 MS. O'DELL: I have an objection.                  7 A Could you -- again, you -- the -- what I                  8 believe has been -- within your statement, but                  9 that's not the reason I believe that the Bradford                  10 Hill criteria are met.                  11 Q (BY MR. ZELLERS) Well, let me ask you a                  12 question.                  13 A Yes.                  14 Q In your discussion of the Bradford Hill                  15 criterion of strength of association, you include                  16 Table 7, which is entitled "An Estimate of the                  17 Number of Ovarian Cancers and Invasive Serous                  18 Cancers Caused by Regular Use of Perineal Talc                  19 Powder Products"; is that right?                  20 A Yes.                  21 Q Is that a calculation that you did to try                  22 to determine whether or not there is strength of                  23 association?                  24 A No, but that's not why I included that.                  25 Q Well, is it included in your "Strength of</p>

<p style="text-align: right;">Page 226</p> <p>1 Association" section?</p> <p>2 A It is included in the strength of</p> <p>3 association to demonstrate how -- an odds ratio of</p> <p>4 1.5, how many patients could be impacted on that.</p> <p>5 So one of the questions is: Is there a</p> <p>6 strong association? And the second, which is really</p> <p>7 quite a different question, is: What's the</p> <p>8 magnitude of that association?</p> <p>9 And sometimes the magnitude of the</p> <p>10 association is mistakenly used as an approximation</p> <p>11 of the strength of the association.</p> <p>12 And I was trying to disentangle the</p> <p>13 strength of the association. How truly do we know</p> <p>14 they're associated with -- if it is associated, how</p> <p>15 big of an impact would it have?</p> <p>16 And so the purpose of Table 7 is not in</p> <p>17 any way to demonstrate the strengths of the</p> <p>18 association, which is a requirement to assess for</p> <p>19 Bradford Hill --</p> <p>20 Q Would your --</p> <p>21 MR. LAPINSKI: She's not finished --</p> <p>22 A -- but how many --</p> <p>23 MR. LAPINSKI: -- Counsel.</p> <p>24 A -- but --</p> <p>25 MR. ZELLERS: Okay. Counsel, one lawyer</p>	<p style="text-align: right;">Page 228</p> <p>1 fine.</p> <p>2 MR. ZELLERS: Please don't interrupt</p> <p>3 the --</p> <p>4 MS. O'DELL: That's --</p> <p>5 MR. ZELLERS: -- deposition.</p> <p>6 MR. LAPINSKI: -- better. Thank you.</p> <p>7 MR. ZELLERS: Ms. O'Dell is doing a</p> <p>8 fabulous job of making objections --</p> <p>9 MR. LAPINSKI: Yes, she is.</p> <p>10 MR. ZELLERS: -- for all of you.</p> <p>11 Q (BY MR. ZELLERS) Okay. Doctor. You were</p> <p>12 trying --</p> <p>13 MS. O'DELL: Excuse me. I don't -- still</p> <p>14 don't think she was finished.</p> <p>15 MR. ZELLERS: Okay.</p> <p>16 MS. O'DELL: So you may continue, Doctor.</p> <p>17 If you were finished, great. If you weren't, you</p> <p>18 may finish your answer.</p> <p>19 A I -- I'm going to have to say I -- I -- so</p> <p>20 the -- the -- Table 7 is an illustration of the</p> <p>21 number of women who would be impacted.</p> <p>22 And the point was to explain that the</p> <p>23 strength of the association is separate from the</p> <p>24 number of women impacted. But indeed, it</p> <p>25 illustrates how important the number of women</p>
<p style="text-align: right;">Page 227</p> <p>1 can object. Okay. I don't want all of you</p> <p>2 objecting.</p> <p>3 MR. LAPINSKI: Don't -- don't raise your</p> <p>4 voice to me.</p> <p>5 MR. ZELLERS: No. I don't want all of you</p> <p>6 objecting.</p> <p>7 MR. LAPINSKI: Counsel, if you want to</p> <p>8 make a statement --</p> <p>9 MR. ZELLERS: Yeah --</p> <p>10 MR. LAPINSKI: -- make a statement.</p> <p>11 MR. ZELLERS: -- I'm making a statement</p> <p>12 that I do not want --</p> <p>13 MR. LAPINSKI: That's --</p> <p>14 MR. ZELLERS: -- the whole group of</p> <p>15 lawyers --</p> <p>16 MR. LAPINSKI: -- and you --</p> <p>17 MR. ZELLERS: -- on the Plaintiffs' side</p> <p>18 objecting.</p> <p>19 MR. LAPINSKI: -- I'm sitting directly</p> <p>20 across the table from you. And I can hear you, and</p> <p>21 I have heard you all day.</p> <p>22 MR. ZELLERS: Okay.</p> <p>23 MR. LAPINSKI: I have heard you carry on</p> <p>24 the way you have carried on all day. There's no</p> <p>25 reason to raise your voice to me. I can hear you</p>	<p style="text-align: right;">Page 229</p> <p>1 impacted is.</p> <p>2 Q Let's go through your math.</p> <p>3 A Yes.</p> <p>4 Q So the table, Table 7, includes several</p> <p>5 assumptions; is that right?</p> <p>6 A A great number of assumptions.</p> <p>7 Q You ran the data, assuming that 10 percent</p> <p>8 of the female population in the United States used</p> <p>9 talcum powder products regularly, as you define</p> <p>10 "regularly"; is that right?</p> <p>11 A Just to clarify, I -- I demonstrated what</p> <p>12 the impact would be if we estimated the number of</p> <p>13 women at 10 percent.</p> <p>14 Q You did the same calculation for</p> <p>15 20 percent and 30 percent; is that right?</p> <p>16 A Yes, I did.</p> <p>17 Q You don't actually know what percentage of</p> <p>18 women use talcum powder products regularly --</p> <p>19 A I --</p> <p>20 Q -- correct?</p> <p>21 A -- I do not.</p> <p>22 Q All right. The calculation -- or your</p> <p>23 conclusion is that .14 percent of women exposed to</p> <p>24 talcum powder products have invasive serous cancer.</p> <p>25 And I am looking at your 10 percent assumption that</p>

<p style="text-align: right;">Page 230</p> <p>1 you make.</p> <p>2 Did you mean .14 or did you mean for that</p> <p>3 to be 14 percent?</p> <p>4 A So I -- I take your correction as a -- as</p> <p>5 correct.</p> <p>6 Q Okay.</p> <p>7 A I do mean 14 percent, but -- but it's not</p> <p>8 the way you have interpreted it.</p> <p>9 The -- the -- the calculation -- the</p> <p>10 columns are the percent of invasive cancer that is</p> <p>11 attributable to talcum powder, not the proportion of</p> <p>12 cancer -- the proportion of women exposed who will</p> <p>13 develop cancer. Those are very different.</p> <p>14 Q I'm not sure I understand. Your column</p> <p>15 here says, The percent of invasive serous cancer in</p> <p>16 women exposed to talcum powder products; is that</p> <p>17 right?</p> <p>18 A That is correct.</p> <p>19 Q Okay. The universe of talcum powder</p> <p>20 products, which you're estimating here -- and I</p> <p>21 understand it's an estimation -- is 10 percent of</p> <p>22 the population; is that right?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A I -- I -- I -- I'm estimating in this</p> <p>25 table that 10 percent of women use talcum powder --</p>	<p style="text-align: right;">Page 232</p> <p>1 women get ovarian cancer. That would be five</p> <p>2 million women.</p> <p>3 I'm saying if we look at the world of</p> <p>4 invasive serous cancers in the United States, there</p> <p>5 will be in the ballpark of 11,000 serous cancers</p> <p>6 every year in the United States.</p> <p>7 Of those, 14 percent of those will occur</p> <p>8 in regular users of talc powders. 86 percent will</p> <p>9 occur in nonregular talc users.</p> <p>10 So you're interpreting what is listed as a</p> <p>11 column percent. It says, Percent of invasive serous</p> <p>12 cancer in women exposed to talc products.</p> <p>13 You're interpreting that as if I'm saying</p> <p>14 that the women exposed, that 15 percent of them will</p> <p>15 get ovarian cancer.</p> <p>16 Q And in fact, if -- if your caption is</p> <p>17 right, if we really are looking at the percent of</p> <p>18 invasive serous cancer in women exposed to talcum</p> <p>19 powder products, it would be less than .01 percent,</p> <p>20 right?</p> <p>21 A Um --</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 A -- you -- you're asking me how many women</p> <p>24 with exposure will end up getting?</p> <p>25 Q (BY MR. ZELLERS) Yes.</p>
<p style="text-align: right;">Page 231</p> <p>1 Q (BY MR. ZELLERS) Right.</p> <p>2 A -- products in the U.S.</p> <p>3 Q There are approximately -- what do you say</p> <p>4 -- 30 --</p> <p>5 A 311 million.</p> <p>6 Q -- all right. So 311 million. And you</p> <p>7 are estimating for purposes of this exercise that</p> <p>8 31,100,000 are regular users; is that right?</p> <p>9 A Yes.</p> <p>10 Q And what you are trying to determine is of</p> <p>11 those 31,100,000, what percent of regular talc users</p> <p>12 will have invasive serous cancer, correct?</p> <p>13 A Yes.</p> <p>14 Q And you have calculated 14 percent; is</p> <p>15 that right?</p> <p>16 A No.</p> <p>17 Q It's wrong, right?</p> <p>18 A The way you are describing it is wrong.</p> <p>19 But I can give you an example to help you understand</p> <p>20 that table.</p> <p>21 Q Well --</p> <p>22 A The number of cancers, we're talking about</p> <p>23 31 million women or women who were exposed to</p> <p>24 cancers.</p> <p>25 I'm not saying 13 -- 14 percent of those</p>	<p style="text-align: right;">Page 233</p> <p>1 A So that's a -- a good number. It's not</p> <p>2 one I presented, but certainly one I can estimate,</p> <p>3 which is -- if we're talking about 31 million women</p> <p>4 who have regular exposure and of those who will</p> <p>5 get -- I'm scribbling on my exhibit. I hope that's</p> <p>6 okay. Is that okay? One, two, three -- one, two,</p> <p>7 three. One -- one out of -- one out of 3,000 women</p> <p>8 will get --</p> <p>9 Q So --</p> <p>10 A -- ovarian cancer.</p> <p>11 Q -- approximately .01 percent, correct?</p> <p>12 A That sounds pretty good, actually.</p> <p>13 Q All right. Dose response. A significant</p> <p>14 number of the talcum powder studies that you looked</p> <p>15 at do not show a dose response or fail to account</p> <p>16 for dose response altogether; is that right?</p> <p>17 A In my summary of dose response on page 39,</p> <p>18 I note that Penninkilampi, one of the large</p> <p>19 meta-analyses, which I think is the most</p> <p>20 comprehensive review, talks about dose response.</p> <p>21 I didn't cite here -- and it was an</p> <p>22 oversight -- Berge, another large comprehensive</p> <p>23 meta-analysis, also shows dose response.</p> <p>24 So the two systematic reviews showed dose</p> <p>25 response. I also list Terry as showing dose</p>



<p style="text-align: right;">Page 234</p> <p>1 response. That's the pool data of a large number of  2 studies. Those are, you know, both quite -- I -- I  3 have covered most of the publications, so those show  4 dose response.  5 There are a few others that I show. There  6 are definitely a bunch that do not address the issue  7 of dose response, but -- but I wouldn't characterize  8 it as most do not.  9 Q Well, you state on page 40 of your report  10 with respect to dose response, The results are  11 inconsistent and more importantly are not considered  12 or assessed in most of the published studies.  13 That was your conclusion with respect to  14 dose response; is that right?  15 A You are going to have to tell me where  16 you're reading. What I'm reading says, In summary,  17 most, but not all, studies of talcum powder products  18 in ovarian cancer show a dose response.  19 THE COURT REPORTER: Slow down when you  20 read, please.  21 A I'm so sorry.  22 In summary, most, but not all, studies of  23 talcum powder products in ovarian cancer show a dose  24 response. Most do.  25 But the results are inconsistent and more</p>	<p style="text-align: right;">Page 236</p> <p>1 A Yes.  2 Q Would you agree that generally when you  3 looked at the published studies, that they showed an  4 association of around 1.3 between perineal talc use  5 and ovarian cancer?  6 A I think many of the studies showed an  7 association of about 1.3 of any talc use. Not  8 quantifying the amount of exposure.  9 Q But would you agree that an -- that  10 epidemiologists generally consider a 1.3 odds ratio  11 in a case-control study to be a weak or modest  12 association?  13 MS. O'DELL: Object to the form.  14 A I am -- I am unaware what -- of what most  15 epidemiologists think.  16 Q (BY MR. ZELLERS) Have you seen any peer  17 reviewed literature on talc and ovarian cancer that  18 states that 1.3 is a strong association?  19 A I mean, Penninkilampi concludes there's a  20 consistent association between perineal talc -- talc  21 use and ovarian cancer.  22 And I'm just looking for how he quantifies  23 that. He concludes the results indicate that  24 perineal talc use is associated with a 24 to  25 39 percent increased risk of ovarian cancer.</p>
<p style="text-align: right;">Page 235</p> <p>1 importantly are not considered assessed in most --  2 that -- that should not say "most." It should say  3 "in many of the published studies."  4 Q (BY MR. ZELLERS) All right. So you would  5 amend your report from "most" to "many; is that  6 right?  7 A I -- I used "most" twice in the same  8 sentence as meaning different things. So yes, I --  9 Q Go --  10 A -- it was an error.  11 Q -- Gertig 2000 study found that there was  12 no increase in risk of ovarian cancer with  13 increasing frequency of use; is that right?  14 A I would have to check that, but I'm happy  15 to do so. I believe that's correct.  16 Q Hunchcharek 2003 found that the data  17 showed a lack of clear dose response relationship,  18 making the relative risk of questionable validity;  19 is that right?  20 A Which -- which one?  21 Q Sure. Hunchcharek 2003, page 19 of 55.  22 A Wait. This one is 2011. I don't -- I  23 don't think I have that one.  24 Q All right. Consistency. Consistency is  25 another factor that you looked at; is that right?</p>	<p style="text-align: right;">Page 237</p> <p>1 He doesn't quantify it as weak or strong,  2 but there's a suggestion that a 39 percent increase  3 is important. But he -- he doesn't quantify it. So  4 I would have to look through the authors'  5 conclusions.  6 Q Do you know who Penninkilampi is?  7 A I do not.  8 Q Do you know that he is a medical student?  9 A I'm very impressed. He did a beautiful  10 review.  11 Q Do you know who Guy Eslick is, the other  12 author on that paper?  13 A I do not.  14 Q Do you know if he's an expert for the  15 Plaintiffs in the talc litigation?  16 A I -- I do not.  17 MS. O'DELL: Object to the form.  18 Q (BY MR. ZELLERS) Does Mr. Eslick disclose  19 or identify that he is working for or has worked for  20 Plaintiffs in the talc litigation?  21 A I might -- I don't know the answer to  22 that.  23 Q You would expect that if that was true,  24 that there would be a disclosure of that; is that  25 right?</p>



<p style="text-align: right;">Page 238</p> <p>1 A I --</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A -- it's published in a very high-impact,</p> <p>4 high-quality medical journal, and I would suspect</p> <p>5 that that would be required of that journal.</p> <p>6 But -- but I -- I -- I -- I don't -- I --</p> <p>7 I don't know that journal's requirements, but I</p> <p>8 would suspect that they would require reporting</p> <p>9 funding.</p> <p>10 Q You --</p> <p>11 A It says -- I'm sorry. It says, The</p> <p>12 authors report no conflicts of interest and have not</p> <p>13 reported funding.</p> <p>14 And typically when you have to reporting</p> <p>15 conflicts of interest in the same area, you also</p> <p>16 report funding, and I don't see any of that.</p> <p>17 Q The cohort studies. There are four cohort</p> <p>18 studies; is that right?</p> <p>19 A Yes.</p> <p>20 Q All right. You rely only on the Gertig</p> <p>21 study, the 2000 study; is that right --</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 Q (BY MR. ZELLERS) -- of those four?</p> <p>24 MS. O'DELL: Excuse me. Object to the</p> <p>25 form.</p>	<p style="text-align: right;">Page 240</p> <p>1 are summarized the way you summarized them. And I</p> <p>2 think if you look at them a little more closely, I</p> <p>3 would not make that conclusion. So --</p> <p>4 Q For the reasons set forth in your report?</p> <p>5 A It's in my report.</p> <p>6 MR. ZELLERS: All right. Let's take a</p> <p>7 break.</p> <p>8 THE VIDEOGRAPHER: We're off the record.</p> <p>9 The time is 3:58 p.m.</p> <p>10 (A break was taken from 3:58 p.m. to</p> <p>11 3:58 p.m.)</p> <p>12 (Next portion not on video record.)</p> <p>13 MR. ZELLERS: So we are back on the</p> <p>14 written record, but not the video record. My</p> <p>15 understanding is that, you know, we are taking a</p> <p>16 break as an accommodation to the witness, and that</p> <p>17 that's fine, but that, you know, you are not going</p> <p>18 to use this time to further meet and prepare the</p> <p>19 witness based upon the questions I asked today.</p> <p>20 MS. O'DELL: Correct. There's --</p> <p>21 there's -- Dr. Smith-Bindman is taking this break</p> <p>22 because she is still recovering from her concussion.</p> <p>23 There will be no meeting with</p> <p>24 Dr. Smith-Bindman. I do want to point out counsel</p> <p>25 for J&amp;J seems to have dictated this requirement in</p>
<p style="text-align: right;">Page 239</p> <p>1 A My report summarizes all four of them, and</p> <p>2 that all went into the weight of my report.</p> <p>3 In terms of being included in any</p> <p>4 systematic review, only one of them was included in</p> <p>5 the systematic review.</p> <p>6 Q (BY MR. ZELLERS) If you looked just at the</p> <p>7 cohort studies --</p> <p>8 A Yes.</p> <p>9 Q -- you would not find a statistically</p> <p>10 significant association between perineal talc use</p> <p>11 and ovarian cancer, correct?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A I --</p> <p>14 MS. O'DELL: Excuse me. When -- when you</p> <p>15 get to a good stopping point, it would be good to</p> <p>16 take a break --</p> <p>17 MR. ZELLERS: Okay.</p> <p>18 MS. O'DELL: -- but whenever you're -- if</p> <p>19 you have a few more minutes, that's fine, but</p> <p>20 whenever you get to a good point.</p> <p>21 A -- so I summarize my view of the cohort</p> <p>22 studies, which are not exactly what you -- what you</p> <p>23 just summarized -- the way you just summarized them</p> <p>24 on page 21.</p> <p>25 So I think that often the cohort studies</p>	<p style="text-align: right;">Page 241</p> <p>1 order to accommodate the witness's situation.</p> <p>2 But I would just note the deposition</p> <p>3 protocol has no such restriction, and -- and so</p> <p>4 that -- to that degree, I would say we have no</p> <p>5 intent to prepare the witness any further.</p> <p>6 But we're not restricted from talking to</p> <p>7 the witness, and I don't want the record to suggest</p> <p>8 otherwise.</p> <p>9 MR. ZELLERS: We will see you tomorrow.</p> <p>10 MS. O'DELL: Thank you.</p> <p>11 THE VIDEOGRAPHER: We are back on the</p> <p>12 record at 4:01 p.m, and this is the end of Disc</p> <p>13 No. 4 in today's testimony of Dr. Rebecca</p> <p>14 Smith-Bindman. The time is 4:01 p.m.</p> <p>15</p> <p>16 (TIME NOTED: 4:01 p.m.)</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

Rebecca Smith-Bindman, M.D.

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1 I, REBECCA SMITH-BINDMAN, M.D., VOLUME I, do  
 2 hereby declare under penalty of perjury that I have  
 3 read the foregoing transcript; that I have made any  
 4 corrections as appear noted, in ink, initialed by  
 5 me, or attached hereto; that my testimony as  
 6 contained herein, as corrected, is true and correct.  
 7 EXECUTED this \_\_\_\_\_ day of \_\_\_\_\_,  
 8 20\_\_\_\_, at \_\_\_\_\_, \_\_\_\_\_.  
 9 (City) (State)

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 15 REBECCA SMITH-BINDMAN, M.D.  
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1 ERRATA SHEET  
 2 Golkow Litigation Services  
 3 1650 Market Street, One Liberty Plaza, 51st Floor  
 4 Philadelphia, Pennsylvania 19103  
 5 877-370-3377

6 CASE: Talcum Powder Litigation

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20  
 21 REBECCA SMITH-BINDMAN, M.D., VOLUME I

22 Subscribed and sworn to before me  
 23 this \_\_\_\_ day of \_\_\_\_\_, 2019.

24 \_\_\_\_\_  
 25 Notary Public

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1 I, MARY J. GOFF, CSR No. 13427, Certified  
 2 Shorthand Reporter of the State of California,  
 3 certify;  
 4 That the foregoing proceedings were taken  
 5 before me at the time and place herein set forth, at  
 6 which time the witness declared under penalty of  
 7 perjury; that the testimony of the witness and all  
 8 objections made at the time of the examination were  
 9 recorded stenographically by me and were thereafter  
 10 transcribed under my direction and supervision; that  
 11 the foregoing is a full, true, and correct  
 12 transcript of my shorthand notes so taken and of the  
 13 testimony so given;  
 14 That before completion of the deposition,  
 15 review of the transcript ( ) was (XX) was not  
 16 requested: ( ) that the witness has failed or  
 17 refused to approve the transcript.  
 18 I further certify that I am not financially  
 19 interested in the action, and I am not a relative or  
 20 employee of any attorney of the parties, nor of any  
 21 of the parties.  
 22 I declare under penalty of perjury under the  
 23 laws of California that the foregoing is true and  
 24 correct, dated this \_\_\_\_ day of \_\_\_\_\_, 2019.  
 25 MARY J. GOFF

Rebecca Smith-Bindman, M.D.

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IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

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IN RE: JOHNSON & JOHNSON TALCUM	)	
POWDER PRODUCTS MARKETING, SALES	)	
PRACTICES, AND PRODUCTS LIABILITY	)	
LITIGATION	)	
	)	MDL No.
	)	2738 (FLW)(LHG)
	)	
	)	

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VIDEOTAPED DEPOSITION OF  
REBECCA SMITH-BINDMAN, M.D.  
San Francisco, California  
Friday, February 8, 2019  
Volume II

Reported by:  
MARY J. GOFF  
CSR No. 13427

Rebecca Smith-Bindman, M.D.

<p style="text-align: right;">Page 246</p> <p>1 2 3 4 5 Videotaped Deposition of REBECCA 6 SMITH-BINDMAN, M.D., Volume II, taken on behalf of 7 Johnson &amp; Johnson, at Levin Simes Abrams LLP, 8 1700 Montgomery Street, Suite 250, San Francisco, 9 California 94111, beginning at 9:26 a.m. and ending 10 at 12:48 p.m., on February 8, 2019, before MARY J. 11 GOFF, California Certified Shorthand Reporter No. 12 13427. 13 14 15 16 17 18 19 20 21 22 23 24 25</p>	<p style="text-align: right;">Page 248</p> <p>1 APPEARANCES (continued): 2 3 For Defendant Johnson &amp; Johnson 4 Tucker Ellis LLP 5 BY: MICHAEL C. ZELLERS 6 Attorney at Law 7 515 South Flower Street 8 42nd Floor 9 Los Angeles, California 90071 10 michael.zellers@tuckerellis.com 11 213-430-3301 12 13 14 For Defendant Johnson &amp; Johnson 15 Skadden, Arps, Slate, Meagher &amp; Flom, LLP. 16 BY: BENJAMIN HALPERIN 17 Attorney at Law 18 4 Times Square 19 New York, New York 10036 20 benjamin.halperin@skadden.com 21 212-735-2453 22 23 24 25</p>
<p style="text-align: right;">Page 247</p> <p>1 APPEARANCES: 2 3 For Plaintiffs 4 Beasley Allen Law Firm 5 BY: P. LEIGH O'DELL 6 MARGARET M. THOMPSON, MD, JD, MPAff 7 Attorney at Law 8 218 Commerce Street 9 Montgomery, Alabama 36103 10 leigh.odell@beasleyallen.com 11 334-269-2343 12 For Plaintiffs 13 Robinson Calcagnie, Inc. 14 BY: CYNTHIA L. GARBER 15 Attorney at Law 16 19 Corporate Plaza Drive 17 Newport Beach, California 92660 18 cgarber@robinsonfirm.com 19 For Plaintiffs 20 Wilentz, Goldman &amp; Spitzer P.A. 21 Daniel R. Lapinski 22 Attorney at Law 23 90 Woodbridge Center Drive, 24 Suite 900 Box 10 25 Woodbridge, New Jersey 07095-0958</p>	<p style="text-align: right;">Page 249</p> <p>1 APPEARANCE (continued): 2 For Defendant Imerys 3 Dykema 4 BY: JANE BOCKUS 5 Attorney at Law 6 112 E. Pecan Street 7 Suite 1800 8 San Antonio, Texas 78205 9 jbockus@dykema.com 10 210-554-5549 11 12 For Defendant Imerys 13 Gordon &amp; Rees LLP 14 BY: JENNIFER A. FOSTER 15 Attorney at Law 16 816 Congress Avenue 17 Suite 1510 18 Austin, Texas 78701 19 jfooster@gordonrees.com 20 512-391-0197 21 22 23 24 25</p>

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<p>1 APPEARANCES (continued):</p> <p>2 For Defendant PCPC, Personal Care Products Council</p> <p>3 Seyfarth Shaw, LLP</p> <p>4 BY: JAMES R. BILLINGS-KANG</p> <p>5 Attorney at Law</p> <p>6 975 F Street, NW</p> <p>7 Washington, D.C. 20004</p> <p>8 jbillingskang@seyfarth.com</p> <p>9 202-828-5356</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14 For Defendants PTI Union, LLC and PTI Royston, LLC</p> <p>15 Tucker Ellis LLP</p> <p>16 BY: CAROLINE M. TINSLEY</p> <p>17 Attorney at Law</p> <p>18 100 South 4th Street</p> <p>19 Suite 600</p> <p>20 St. Louis, Missouri, 63102</p> <p>21 caroline.tinsley@tuckerellis.com</p> <p>22</p> <p>23 Videographer:</p> <p>24 Andrew Graves</p> <p>25</p>	<p>1 EXHIBITS CONTINUED: PAGE</p> <p>2 Exhibit 34 Does Exposure to Asbestos Cause 324</p> <p>3 Ovarian Cancer article</p> <p>4 Exhibit 35 Occupational Exposure to Asbestos 327</p> <p>5 article</p> <p>6</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
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<p>1 INDEX</p> <p>2 WITNESS EXAMINATION</p> <p>3 REBECCA SMITH-BINDMAN, M.D.</p> <p>4 Volume II</p> <p>5</p> <p>6 BY MR. ZELLERS 254, 372</p> <p>7 BY MS. O'DELL 354</p> <p>8 BY MR. BILLINGS-KANG 347</p> <p>9 BY MS. BOCKUS 331, 369</p> <p>10</p> <p>11 NUMBER DESCRIPTION PAGE</p> <p>12 Exhibit 28 6/1/17 Letter, Invoice 259</p> <p>13</p> <p>14 Exhibit 29 Bill, Invoice 147 261</p> <p>15</p> <p>16</p> <p>17 Exhibit 30 Perineal Use of Talc and Risk 276</p> <p>18 of Ovarian Cancer article</p> <p>19</p> <p>20 Exhibit 31 Influence of Aspirin and nonaspirin 297</p> <p>21 NSAID Use article</p> <p>22</p> <p>23 Exhibit 32 Article, Talc 317</p> <p>24</p> <p>25 Exhibit 33 Invoice, Tachibana, UCSF, 10/18 319</p>	<p>1 San Francisco, California</p> <p>2 February 8, 2019</p> <p>3 9:26 a.m.</p> <p>4</p> <p>5 THE VIDEOGRAPHER: We are now on the</p> <p>6 record. My name is Andrew Graves. I'm a</p> <p>7 videographer for Golkow Litigation Services.</p> <p>8 Today's date is February 8, 2019. The time is</p> <p>9 9:26 a.m.</p> <p>10 This video deposition is being held at</p> <p>11 1700 Montgomery Street, Suite 250, San Francisco,</p> <p>12 California, In the Matter of In Re: Johnson &amp;</p> <p>13 Johnson Talcum Powder Products Marketing, Sales</p> <p>14 Practices, and Products Liability Litigation, for</p> <p>15 the United States District Court, District of</p> <p>16 New Jersey.</p> <p>17 The deponent is Rebecca Smith-Bindman,</p> <p>18 Ph.D., Volume II.</p> <p>19 Would counsel please identify yourselves.</p> <p>20 MR. ZELLERS: Can we waive that since we</p> <p>21 were all here yesterday?</p> <p>22 THE VIDEOGRAPHER: Okay. The court</p> <p>23 reporter is Mary Goff, and she will now swear in the</p> <p>24 witness.</p> <p>25</p>

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<p style="text-align: right;">Page 254</p> <p>1 REBECCA SMITH-BINDMAN, M.D., VOLUME II, 2 being first duly sworn or affirmed to testify to the 3 truth, the whole truth, and nothing but the truth, 4 was examined and testified as follows: 5 EXAMINATION BY COUNSEL FOR THE DEFENDANTS 6 BY MR. ZELLERS: 7 Q Good morning. 8 A Good morning. 9 Q Dr. Smith-Bindman, did you do anything to 10 prepare -- or further prepare for your deposition 11 since the time we concluded yesterday and this 12 morning? 13 A I did two things. I reviewed my report 14 again, and I called the biostatistician who worked 15 on my meta-analysis to review a few of the details. 16 Q You called Dr. Hall? 17 A I did. 18 Q When was the last time that you had talked 19 with Dr. Hall before yesterday? 20 A Speaking to her at the time of -- that she 21 did the analysis. And I -- I think there was an 22 e-mail or two over the last several weeks asking for 23 her CV or something like that, but not any 24 meaningful conversation. 25 Q Have you produced the e-mails -- the</p>	<p style="text-align: right;">Page 256</p> <p>1 manuscript. 2 I was quite surprised that they weren't 3 exactly the same. They were not meaningfully 4 different, but there was a very slight shift in 5 the ones that are in my report. 6 I mean, I asked Dr. Jane why that was the 7 case. And in fact, the numbers are calculated using 8 the standard errors in the confidence intervals and 9 the sample size which very slightly shifts it from 10 the reported numbers. 11 So you were correct when you said the 12 numbers are not exactly the same, and she explained 13 that that's why that's the case. 14 Q Are the numbers that were contained in 15 Figure -- Figures 2 and 3 in your report, estimates? 16 MS. O'DELL: Object to the form. 17 A The numbers are calculated. So I -- I 18 think by that, you mean estimates. 19 Q (BY MR. ZELLERS) Did you do the 20 calculations? 21 A No. She -- she did them. 22 Q Do we -- 23 THE COURT REPORTER: Can you raise your 24 voice for me, please? 25 A Yes, I can. I apologize.</p>
<p style="text-align: right;">Page 255</p> <p>1 recent e-mails with Dr. Hall? 2 A I -- I'm not sure if I produced the one 3 asking for her CV, but the -- and actually, I don't 4 remember when I asked her for that. I might have 5 presented -- 6 MS. O'DELL: I think that's part of the 7 production -- 8 Q (BY MR. ZELLERS) How -- 9 MS. O'DELL: -- but -- excuse me. 10 Q (BY MR. ZELLERS) How long did you speak 11 with Dr. Hall yesterday? 12 A About 15 -- 10-15 minutes. 13 Q Did you make any written notes? 14 A I -- I think I scribbled in my usual 15 scribble place. 16 Q What notes did you make from your 17 conversation with Dr. Hall yesterday after the first 18 session of your deposition? 19 A So -- so I did -- I did -- I did jot some 20 notes on my meta-analysis. But mostly I asked her 21 to clarify how she did the calculations of the 22 numbers that are shown in the figures. 23 I was struggling to understand why the 24 numbers and the figures were not exactly the same as 25 the ones that you showed me in the published</p>	<p style="text-align: right;">Page 257</p> <p>1 Q (BY MR. ZELLERS) Do we have her work 2 product as to the calculations that were made? 3 A In the documents that I shared, she 4 specified the -- the software that she used, the 5 program that she used. 6 In fact, the way of estimating it, it's 7 actually in my report as well. And so yes, it's 8 explained there, and it's in all of the documents 9 that I shared with you. 10 Q Her calculations are contained in the 11 documents that are shared; is that right? 12 A Yes. 13 Q The numbers that you got from the Terry 14 study, those came from the Terry publication; is 15 that right? 16 A Yes. 17 Q Any additional notes you made from your 18 discussion with Dr. Hall, other than what you have 19 generally told us about? 20 A No. Just that. 21 Q The notes that you added to your annotated 22 report from your discussion with Dr. Hall, which we 23 marked as Exhibit 17, those notes are on which page 24 or pages? 25 A Page 33 and 34.</p>

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<p>1 Q It looks like you made those notes in an 2 aqua pen is -- is that right, or -- 3 A Yes. 4 Q -- I -- 5 A Yes. 6 Q Okay. 7 A Yes, absolutely. 8 Q Any -- 9 A I would say teal, but... 10 Q Well, I think you're probably more correct 11 than I am. 12 Any other notes that you had from your 13 discussion with Dr. Hall? 14 A No. 15 Q Any other communications that you had with 16 Dr. Hall, other than your 10- or 15-minute phone 17 conversation yesterday afternoon or evening? 18 A No. 19 Q Did you communicate with Dr. Hall via 20 e-mail or any way other than just the phone call? 21 A No. 22 Q Did you communicate with anyone else 23 between the time we finished yesterday and this 24 morning about the subject matter that we're here to 25 talk about?</p>	<p>1 Q What do you -- well, I will take that as a 2 yes, that at least through November 13, 2018, that 3 Deposition Exhibit 28 are all of your invoices -- 4 A Yeah. 5 Q -- is that right? 6 A Yes. 7 Q Those invoices total approximately 8 160 hours. Does that sound right? 9 A 160? 10 Q 160. 11 A I'm -- I'm going to believe you. 12 Q Well, and anyone can go and check my math. 13 How many hours do you estimate that you 14 have spent up until today on this matter both doing 15 additional work, reviewing those additional studies 16 and materials we talked about yesterday, preparing 17 for the deposition, meeting with counsel for 18 Plaintiffs? 19 MS. O'DELL: Since the last invoice? 20 MR. ZELLERS: Since the last invoice is 21 what I had intended to ask. 22 MS. O'DELL: Yeah. Thank you. 23 A I -- I think approximately 25 hours. 24 Q (BY MR. ZELLERS) In addition, we were 25 provided with a two-page exhibit which are two</p>
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<p>1 A No. 2 Q At the start of the session today, counsel 3 for Plaintiffs, Ms. O'Dell, provided me with copies 4 of your invoices. 5 I'm going to hand you what we have marked 6 as Exhibit 28. It is a five-page exhibit. 7 The first page is a cover letter. It 8 looks like an engagement or general engagement 9 letter from you to -- you say Mr. Carmen Scott. 10 Is it a Ms. Carmen Scott? 11 (Exhibit 28 was marked for identification 12 and is attached to the transcript.) 13 A It is. 14 Q All right. That was on June 1 of 2017. 15 The last invoice is November 13 of 2018; is that 16 right? 17 A I'm sorry. What was the question? Is 18 this -- 19 Q The question is: Are those all of our 20 invoices that you have generated thus far in the 21 talcum powder MDL litigation? 22 A I -- I think I mentioned that there are -- 23 I haven't submitted anything beyond this, but that 24 there are additional hours that I recorded after 25 this.</p>	<p>1 invoices from Jane Hall, which total around \$3,000. 2 (Exhibit 29 was marked for identification 3 and is attached to the transcript.) 4 Q (BY MR. ZELLERS) Can you look at 5 Exhibit 29 and verify for us that those are the 6 e-mails -- strike that -- that those are the 7 invoices for the work that was done by Dr. Hall? 8 A I -- I -- I believe so. 9 Q Are you aware of any additional invoices 10 beyond that? 11 A I'm not. 12 Q Do you have any invoices from your copy 13 editor, Ms. Tachibana? 14 A She sent me an invoice, which I forwarded 15 to counsel. 16 Q All right. How much was that invoice for? 17 A I think it was about \$1,500. 18 Q How much an hour does Ms. Tachibana 19 charge? 20 A I think it's about a hundred dollars an 21 hour. 22 Q Was that for all of the work that she did 23 with respect to your report? 24 A Yes. There was no other work other than 25 that 15 -- it might have been \$1,700.</p>

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<p>1 MS. O'DELL: Excuse me. I'm sorry, Mike. 2 I apologize for not copying that. We're going to 3 make a copy, and I will provide it to your 4 momentarily at -- 5 MR. ZELLERS: Very good. We'll mark it 6 before the conclusion of the deposition. Thank you. 7 Q (BY MR. ZELLERS) Do you have your report 8 in front of you? You can use your annotated 9 version, No. -- Exhibit 17. We also marked your 10 report as Exhibit 2. 11 A Yes. 12 Q Do you have that in front of you? 13 A I do. 14 Q Go to page 17, if you will, please. 15 MR. LAPINSKI: Counsel, you said page 17? 16 MR. ZELLERS: Yes, page 17. 17 A Yes. 18 Q (BY MR. ZELLERS) On page 17, you make a 19 number of general statements about the advantages 20 and disadvantages of case control and cohort 21 studies; is that right? 22 A Yes. 23 Q There are no citations there. Is this 24 based and those statements based on your general 25 knowledge?</p>	<p>1 paragraph, Mike? I have lost track. 2 MR. ZELLERS: I was asking about the 3 specific statement in the middle paragraph of 4 page 17 relating to cohort studies and the 5 limitation that they rarely focus on a single 6 narrowly defined question. 7 MS. O'DELL: Yes. Thank you. 8 Q (BY MR. ZELLERS) But my question now is -- 9 A Yes. 10 Q -- whether or not Dr. Smith-Bindman, as 11 you sit here, can cite any published literature that 12 states the cohort studies are unlikely to detect a 13 real association -- or unlikely to detect real 14 associations for this reason. 15 A I -- 16 MS. O'DELL: Excuse me. Are you 17 quoting -- when you say "unlikely to detect real 18 associations for this reason," is that reading -- 19 are you reading from her report or is that just -- 20 MR. ZELLERS: No. That's my question. 21 MS. O'DELL: -- okay. Sorry. 22 MR. ZELLERS: And if it's not very 23 articulate -- 24 A I -- I think cohort -- cohort studies are 25 able to detect real associations, if they ask about</p>
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<p>1 A Yes. This is based on Epi 101, sort of... 2 Q You make a statement in the middle 3 paragraph on page 17 where you talk about "cohort 4 studies." 5 And you state that they rarely focus on a 6 single narrowly defined question and that that's an 7 important limitation of cohort studies. 8 Do you see that? 9 A I do. 10 Q Can you cite to any other epidemiologists 11 who agree with you on that point? 12 A So it's very well known the cost of doing 13 a cohort study is often very large, and so the topic 14 that's often the central focus of the cohort study 15 is very, very well done. 16 It's the ancillary topics that often get 17 short shrift. And so that -- I -- I could probably 18 find this explained in any basic textbook. 19 And -- and I -- I apologize for not citing 20 it. This is sort of just very well-known general 21 concepts of study design. 22 Q Can you cite to any published literature 23 that states that cohort studies are unlikely to 24 detect real associations for this reason? 25 MS. O'DELL: Are you reading a particular</p>	<p>1 those associations. 2 If they don't ask about it, then it 3 can't -- then -- then it doesn't have an ability to 4 measure it. 5 So what I am saying here is that cohort 6 studies don't have the capacity to go in depth and 7 ask. 8 I think all of the cohort studies that I 9 reviewed for -- for this review discuss the lack of 10 detail in the cohort question, meaning that it's not 11 that the study design was the problem. It was that 12 they just didn't have the right predictor 13 information being assessed. 14 Q Despite this limitation -- or in your 15 view, limitation of cohort studies, you did include 16 the Gertig 2000 cohort study in your systematic 17 review; is that right? 18 A I did. I just want to clarify the answer. 19 Cohort studies are a very strong study design that I 20 like very much and that I have used and currently 21 I'm -- I'm using in study designs. 22 It's rather if the study design uses a 23 cohort, which is a good design, doesn't have enough 24 detail, because that's not the focus, that 25 doesn't -- it can't be used to answer other</p>

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<p>1 questions easily.</p> <p>2 So I think in general I like cohort</p> <p>3 designs very much, and I think it's a very powerful</p> <p>4 study design. But if you haven't asked the right</p> <p>5 questions, it's hard to the expand it.</p> <p>6 So I did -- I read all of the cohorts on</p> <p>7 this topic.</p> <p>8 Q And you concluded that the Gertig cohort</p> <p>9 study, you know, asked the right information or had</p> <p>10 sufficient information for you to include it both in</p> <p>11 your general systematic review and in your more</p> <p>12 focused systematic review which you set forth as</p> <p>13 Figures 2 and 3 in your report, correct?</p> <p>14 A That's correct. That -- those -- those</p> <p>15 were looking at regular use, and I thought the</p> <p>16 Gertig was the cohort that allowed me to understand</p> <p>17 regular use of perineal talc.</p> <p>18 Q Gertig was based on the Nurses' Health</p> <p>19 Study; is that right?</p> <p>20 A Yes.</p> <p>21 Q Gertig and the authors do recognize that</p> <p>22 the biologic evidence for the association of talc</p> <p>23 and ovarian cancer is incomplete, correct?</p> <p>24 MS. O'DELL: Object to the form.</p> <p>25 A I -- I don't have it in front of me, but</p>	<p>1 yet they didn't report it that way.</p> <p>2 They only reported on any exposure to talc</p> <p>3 powder products. And that is a very vague</p> <p>4 definition as opposed to the frequency of use.</p> <p>5 And for that reason, I couldn't tell in --</p> <p>6 in nearly the same detail as I could for the earlier</p> <p>7 study, the -- the exposure. They just chose not to</p> <p>8 present it that way.</p> <p>9 Q The Gates 2010 cohort study did include</p> <p>10 over a hundred thousand women; is that right?</p> <p>11 A The Gates?</p> <p>12 Q Yes.</p> <p>13 A It was large, but I need to check the</p> <p>14 actual numbers.</p> <p>15 Q Here. Let me hand it to --</p> <p>16 A I have it. I have it.</p> <p>17 Q Do you have it?</p> <p>18 A Yeah.</p> <p>19 Q Okay. And I am looking at page 47. And</p> <p>20 it's quoting the Nurses' Health Study as involving</p> <p>21 close to 109,000 --</p> <p>22 A I'm not sure.</p> <p>23 Q -- women?</p> <p>24 A I'm not sure. I'm looking at the -- the</p> <p>25 Gates -- are you asking about Gates or Gertig?</p>
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<p>1 it may be that they reported as of 2000, they didn't</p> <p>2 have evidence of the biologic mechanism. I --</p> <p>3 Q And I will ask you about biologic</p> <p>4 mechanism before we conclude here today.</p> <p>5 You did not, though -- well, let me</p> <p>6 withdraw that.</p> <p>7 There was a follow-up cohort study to</p> <p>8 Gertig 2000, and that was the Gates 2010 cohort</p> <p>9 study; is that right?</p> <p>10 A Yes.</p> <p>11 Q That had a longer follow-up than Gertig;</p> <p>12 is that right?</p> <p>13 A Yes.</p> <p>14 Q It was an analysis of the data collected</p> <p>15 in the Nurses' Health Study; is that right?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A It was analysis of some of the data</p> <p>18 collected in the -- in the Nurses' Health Study, but</p> <p>19 they did not report the variable in such a way that</p> <p>20 would allow you to understand or to quantify the</p> <p>21 exposure as opposed to the first cohort study which</p> <p>22 did.</p> <p>23 So the latter study, they -- they had the</p> <p>24 data, which is why I'm answering it this way. They</p> <p>25 clearly had it, because the data hadn't change, and</p>	<p>1 Q I'm asking about Gates 2010.</p> <p>2 A In mine it says \$221,000 woman with 924</p> <p>3 epithelial ovarian cancer.</p> <p>4 Am I looking in the wrong place?</p> <p>5 Q No. I -- and then if you look further, it</p> <p>6 talks about -- at least in the Nurses' Health Study,</p> <p>7 there being 108,870 women; is that right?</p> <p>8 A Yes.</p> <p>9 Q The women in the national health study,</p> <p>10 which was the basis for both the Gertig 2000 cohort</p> <p>11 study and Gates 2010 cohort study, those women were</p> <p>12 followed from 1976 to 2006, so for 30 years --</p> <p>13 A Yes.</p> <p>14 Q -- is that right?</p> <p>15 A Yes.</p> <p>16 Q And -- and after following these hundred</p> <p>17 thousand women -- or over hundred thousand women for</p> <p>18 three decades, the authors in Gates 2010 concluded</p> <p>19 that the data did not show a statistically</p> <p>20 significant relationship between talcum powder use</p> <p>21 and any type of epithelial ovarian cancer; is -- is</p> <p>22 that right?</p> <p>23 A The Gates authors concluded that there was</p> <p>24 no association between any talcum powder product</p> <p>25 use, and it was not significant in ovarian cancer,</p>

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<p style="text-align: right;">Page 270</p> <p>1 yes.</p> <p>2 Q Another short study that you did not</p> <p>3 include in your systematic review was the Houghton</p> <p>4 study; is that right?</p> <p>5 MS. O'DELL: Object to form.</p> <p>6 A Yes, that is true.</p> <p>7 Q (BY MR. ZELLERS) The Houghton study was</p> <p>8 based on -- or is also called the Women's Health</p> <p>9 Initiative Study; is that right?</p> <p>10 A Yes, it is.</p> <p>11 Q That involved 61,000 women; is that right?</p> <p>12 A That is correct.</p> <p>13 Q Houghton 2014 did not find a statistically</p> <p>14 significant relationship between perineal talc use</p> <p>15 and ovarian cancer among women who had ever used</p> <p>16 talc; is that right?</p> <p>17 A That is what they concluded.</p> <p>18 Q Or among women who had fewer than nine</p> <p>19 years of perineal talc use, correct?</p> <p>20 A Correct.</p> <p>21 Q Or among women who had more than 10 years</p> <p>22 of perineal talc use, correct?</p> <p>23 A Can you say that last part?</p> <p>24 Q Sure.</p> <p>25 A Sorry.</p>	<p style="text-align: right;">Page 272</p> <p>1 using it on a -- on a frequent basis, so I think the</p> <p>2 duration is very different measure.</p> <p>3 Q We talked yesterday about your definition</p> <p>4 of "regular use," and you pointed me to your report</p> <p>5 where you give an extensive discussion of that.</p> <p>6 Do you remember?</p> <p>7 A I do.</p> <p>8 Q Did -- your definition of "regular use,"</p> <p>9 was that every psychometrically tested to</p> <p>10 demonstrate any validity or reliability?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A Of -- are you asking about the reliability</p> <p>13 of the way we defined it --</p> <p>14 Q (BY MR. ZELLERS) Yes.</p> <p>15 A -- or about the concept?</p> <p>16 Q No. About the way you defined it.</p> <p>17 A I believe we explained in the report that</p> <p>18 we tried to approximate regular use, frequency use</p> <p>19 by being at least three times a week and as close to</p> <p>20 daily as possible.</p> <p>21 But in terms of -- if that is -- I -- I'm</p> <p>22 not -- we have not validated that in different</p> <p>23 studies or --</p> <p>24 Q That's something that you came up with; is</p> <p>25 that right?</p>
<p style="text-align: right;">Page 271</p> <p>1 Q Houghton 2014, that cohort study --</p> <p>2 A Okay. No. I -- yes, that is correct.</p> <p>3 Q And also, they did not find a</p> <p>4 statistically significant relationship between</p> <p>5 perineal talc use -- strike that.</p> <p>6 They also did not find a statistically</p> <p>7 significant relationship between the use of talcum</p> <p>8 powder on sanitary napkins or diaphragms on -- and</p> <p>9 ovarian cancer; is that right?</p> <p>10 A That's correct.</p> <p>11 Q Houghton does report on duration of use at</p> <p>12 least more than 10 years of use; is that right?</p> <p>13 A Yes.</p> <p>14 Q But would you consider women who use</p> <p>15 talcum powder for more than 10 years to be frequent</p> <p>16 talc users?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A So you're asking if duration of use can be</p> <p>19 equated with frequency of use, and -- and I would</p> <p>20 very strongly disagree that those are equivalent.</p> <p>21 And that is the primary reason that I</p> <p>22 discount the results of the Gonzalez and Houghton</p> <p>23 and Gates studies.</p> <p>24 Because frequency of use, meaning to use</p> <p>25 it once a month or once a year, is not the same as</p>	<p style="text-align: right;">Page 273</p> <p>1 A Yeah.</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A Yes, it is.</p> <p>4 Q (BY MR. ZELLERS) Gonzalez. You criticize</p> <p>5 Gonzalez in your report for combining various types</p> <p>6 of use. Do you recall that generally? So that's</p> <p>7 page 21 where --</p> <p>8 A No. I'm -- I'm on my report. My -- my</p> <p>9 hesitation is it's not so much that I'm criticizing</p> <p>10 the study. It's rather it doesn't contribute to</p> <p>11 answering the question that I was asking, which was:</p> <p>12 Does regular perineal talc exposure increase the</p> <p>13 risk?</p> <p>14 It doesn't mean that the questions they</p> <p>15 have asked are not interesting questions. They were</p> <p>16 just not the ones I was focusing on.</p> <p>17 Q Why would combining various types of use,</p> <p>18 bias the results in favor of not detecting an</p> <p>19 association?</p> <p>20 I guess from your statement it -- it may</p> <p>21 well not bias the results; is that right? It just</p> <p>22 was just a different question --</p> <p>23 A It's just a different question.</p> <p>24 Q -- than what --</p> <p>25 A I --</p>

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<p style="text-align: right;">Page 274</p> <p>1 Q -- you were looking at?</p> <p>2 A -- I believe that you want to have as</p> <p>3 narrow a definition, in my belief, of meta-analysis</p> <p>4 as possible to understand when you're pooling</p> <p>5 results, make sure -- something you said -- you're</p> <p>6 combining apples to apples.</p> <p>7 And I think one would expect that any</p> <p>8 potential -- potential exposure to talcum powder</p> <p>9 would matter what skin or surface or cell line or</p> <p>10 tissue you're putting against, and you wouldn't</p> <p>11 necessarily expect the same result in a cervical</p> <p>12 exposure or a diaphragm exposure or a vaginal</p> <p>13 exposure.</p> <p>14 You -- you might have an association of</p> <p>15 those places. You might not. I just think it's a</p> <p>16 different question.</p> <p>17 Q All of the cohort studies were prospective</p> <p>18 as opposed to retrospective; is that right?</p> <p>19 A Yes.</p> <p>20 Q Prospective studies are not subject to</p> <p>21 recall bias like retrospective studies, correct?</p> <p>22 A Yes, that's true.</p> <p>23 Q They're also not subject to the same</p> <p>24 selection bias as retrospective studies, correct?</p> <p>25 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 276</p> <p>1 absolutely that's a possibility.</p> <p>2 Q You also looked at both the hospital-based</p> <p>3 and the population-based case-control studies; is</p> <p>4 that right?</p> <p>5 A I did.</p> <p>6 Q None of the hospital-based case-control</p> <p>7 studies show a statistically significant association</p> <p>8 between talc use and ovarian cancer, correct?</p> <p>9 A I -- I'm not sure --</p> <p>10 Q Take a look at --</p> <p>11 A -- where you're getting that from.</p> <p>12 Q I will show you the Langseth paper from</p> <p>13 2008, which you cite and we talked about yesterday.</p> <p>14 Let's mark this as Exhibit 30.</p> <p>15 (Exhibit 30 was marked for identification</p> <p>16 and is attached to the transcript.)</p> <p>17 A I have it. I have it.</p> <p>18 Q (BY MR. ZELLERS) All right. Now -- and</p> <p>19 let me just -- I'll put it in the record there.</p> <p>20 MS. O'DELL: Thank you.</p> <p>21 Q (BY MR. ZELLERS) If you look at the</p> <p>22 Langseth paper, on the second page, Figure 1, they</p> <p>23 list out all of the population -- or at least a</p> <p>24 great number of the population-based and</p> <p>25 case-control studies and the hospital-based</p>
<p style="text-align: right;">Page 275</p> <p>1 A In general, case-control studies are often</p> <p>2 plagued with selection bias, but they don't have to</p> <p>3 be.</p> <p>4 Q (BY MR. ZELLERS) Well, recall bias can</p> <p>5 distort a scientific evaluation of whether an</p> <p>6 exposure is actually related to a disease, correct?</p> <p>7 A Yes.</p> <p>8 Q So for example, recall bias could distort</p> <p>9 results if women with ovarian cancer were more</p> <p>10 likely to remember their exposure to talc than women</p> <p>11 without ovarian cancer; is that right?</p> <p>12 A That is a theoretical risk.</p> <p>13 Q In fact, in your report on page 17, you</p> <p>14 acknowledge that the risk of bias is greater for</p> <p>15 case-control studies as opposed to cohort studies;</p> <p>16 is that right?</p> <p>17 A Yes.</p> <p>18 Q Recall bias could explain the fact that</p> <p>19 some retrospective case-control studies have found a</p> <p>20 statistically significant relationship between</p> <p>21 talcum powder and ovarian cancer, but the cohort</p> <p>22 studies have not, correct?</p> <p>23 A That is a theoretical risk. To do that</p> <p>24 you would need to have some knowledge in the</p> <p>25 population that influenced that recall bias, but</p>	<p style="text-align: right;">Page 277</p> <p>1 case-control studies; is that right?</p> <p>2 A Yes, they do.</p> <p>3 Q (BY MR. ZELLERS) At least among the</p> <p>4 hospital-based case-control studies that are</p> <p>5 identified by Langseth in Figure 1, it appears that</p> <p>6 there's six hospital-based case-control studies.</p> <p>7 None of those hospital-based case-control</p> <p>8 studies show a statistically significant</p> <p>9 association, correct?</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A We discussed this yesterday. But if</p> <p>12 you're asking if the individual hospital-based</p> <p>13 studies overlap one, then they overlap one.</p> <p>14 Q (BY MR. ZELLERS) They do not overlap one?</p> <p>15 A The -- the hospital-based studies do</p> <p>16 overlap one.</p> <p>17 Q Okay. The population-based case-control</p> <p>18 studies, which are up above in our</p> <p>19 Langseth Figure 1, some of those -- if we look at</p> <p>20 the individual studies -- show statistical</p> <p>21 significance, and some of those do not; is that</p> <p>22 right?</p> <p>23 A I'm -- I'm hesitant to be as definitive</p> <p>24 about using the confidence interval that are</p> <p>25 presented here as being a reflection of statistical</p>

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<p style="text-align: right;">Page 278</p> <p>1 significance.</p> <p>2 All of them are shifted to the right. All</p> <p>3 of them have a positive association. And the</p> <p>4 confidence interval for some of them overlap one.</p> <p>5 But taken as a group, there's statistical</p> <p>6 significance for the entirety of the population --</p> <p>7 of the population of studies that he looked at.</p> <p>8 Q As we did discuss yesterday, if you look</p> <p>9 at the population-based studies individually, at</p> <p>10 least based upon what's reported by Langseth in his</p> <p>11 Figure 1, some demonstrate statistical significance</p> <p>12 and some do not; is that right?</p> <p>13 A I -- again, it's -- they're slightly --</p> <p>14 it's -- it's not the only -- the confidence interval</p> <p>15 overlapping one is sort of what I consider a</p> <p>16 quick-and-dirty way to answer statistical</p> <p>17 significance.</p> <p>18 It's not exactly that way. But some of</p> <p>19 them clearly suggest statistical significance. I</p> <p>20 think ten of them. And four of them suggest not</p> <p>21 statistical significance. So the individual</p> <p>22 studies. But it's a little more complicated than</p> <p>23 that.</p> <p>24 Q Would you agree that if a study does not</p> <p>25 show statistical significance, that it could mean</p>	<p style="text-align: right;">Page 280</p> <p>1 tell if things are different or the -- or</p> <p>2 indistinguishable, the confidence interval for the</p> <p>3 pooled odds ratio for the population-based studies</p> <p>4 goes from 1.29 to 1.52, so the truth is likely in</p> <p>5 that range, where the truth for the hospital-based</p> <p>6 studies is 0.92 to 1.63. They overlap.</p> <p>7 And so I would interpret that using this</p> <p>8 sort of quick approach is that there's not a</p> <p>9 statistical difference between the summary of the</p> <p>10 pooled odd ratio based on the type of populations</p> <p>11 that were recruited.</p> <p>12 Again, the point estimates are a little</p> <p>13 bit different for sure, 1.4 versus 1.12. But the</p> <p>14 confidence intervals overlap, suggesting that</p> <p>15 they're not -- they're not different.</p> <p>16 Q You are familiar with selection bias; is</p> <p>17 that right?</p> <p>18 A I am.</p> <p>19 Q Would you agree that the hospital-based</p> <p>20 case-control studies may be less susceptible to</p> <p>21 selection bias than population-based case-control</p> <p>22 studies?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A I -- I would not agree with that. In</p> <p>25 general, you think about hospital-based studies as</p>
<p style="text-align: right;">Page 279</p> <p>1 that no risk exists?</p> <p>2 A If --</p> <p>3 MS. O'DELL: Object to the form.</p> <p>4 A -- an individual study shows no</p> <p>5 statistical significance, it means -- with all</p> <p>6 research -- that the most likely truth is the point</p> <p>7 estimate, which is whatever that point estimate is,</p> <p>8 but that you could not exclude chance as one of the</p> <p>9 possible causes for the results.</p> <p>10 Q (BY MR. ZELLERS) If we looked just at the</p> <p>11 population-based case-control studies and the</p> <p>12 hospital-based case-control studies that are shown</p> <p>13 by Langseth in Figure 1, there is an inconsistency</p> <p>14 between the two in that each of the individual</p> <p>15 hospital-based case-control studies have confidence</p> <p>16 intervals which overlap one, and many of the</p> <p>17 population-based or at least some of the</p> <p>18 population-based studies do not, correct?</p> <p>19 A I -- I do not believe there is</p> <p>20 inconsistency between the pooled odds ratio for</p> <p>21 population-based studies, which has a confidence</p> <p>22 interval that overlaps the confidence intervals for</p> <p>23 the pooled odd ratio for the hospital-based studies.</p> <p>24 So using the approach that you are</p> <p>25 suggesting of using confidence intervals, the way to</p>	<p style="text-align: right;">Page 281</p> <p>1 being potentially a great deal more bias.</p> <p>2 Now, that -- with that caveat, it depends</p> <p>3 on how you found your cases and your controls.</p> <p>4 But in general, you want to find</p> <p>5 population-based cases and controls, I believe,</p> <p>6 rather than hospital-based. But it matters how they</p> <p>7 are recruited.</p> <p>8 Q Hospital-based control studies are</p> <p>9 comparing hospitalized patients to hospitalized</p> <p>10 patients; is that right?</p> <p>11 A I -- I -- in this case, yes, I think</p> <p>12 that's --</p> <p>13 Q And --</p> <p>14 A -- how they define it.</p> <p>15 Q -- in population based studies, you're</p> <p>16 more likely to be comparing ill people to healthy</p> <p>17 people; is that right?</p> <p>18 A Again, it -- it depends on how you're</p> <p>19 selecting. If you're selecting patients who are</p> <p>20 sick in the hospital and comparing that to healthy</p> <p>21 patients who are outpatient population based, that</p> <p>22 would be the kind of bias that you are describing.</p> <p>23 That would be the worst.</p> <p>24 But if you're, in fact, comparing</p> <p>25 relatively comparable population-based cases and</p>

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<p style="text-align: right;">Page 282</p> <p>1 controls, then I don't agree that hospital-based 2 controls are -- are better. 3 Q Penninkilampi. One of the studies that 4 you talked to us about yesterday was Penninkilampi 5 2018; is that right? 6 A Yes. 7 Q Penninkilampi 2018 did not include the 8 Gates 2010 cohort study; is that right? 9 A That's correct. 10 Q Did you verify that the data that 11 Penninkilampi reports is accurate? 12 A I did not. Did I go back and validate 13 their individual abstracted data? 14 Q Yeah. 15 A I did not. 16 Q In determining that a study is of high 17 quality, would it be important to you that the 18 authors are accurately reporting the odds ratios and 19 confidence intervals? 20 A Data accuracy is important to me. And -- 21 and I would look towards the journal peer review 22 process to have done that, yes. 23 Q If -- if there were errors in reporting of 24 the odds ratios or the confidence intervals, that 25 could call into question the reliability of the</p>	<p style="text-align: right;">Page 284</p> <p>1 been established; is that right? 2 A That is what they say. 3 Q Meta-analyses or systematic analyses, that 4 can combine the work of other published studies into 5 one study; is that right? 6 A Yes. 7 Q If there are biases and confounding in the 8 underlying studies, the meta-analysis or the 9 systematic review or analysis will reflect the 10 biases and confounding; is that right? 11 MS. O'DELL: Object to the form. 12 A Any biases in the papers will not go away 13 by combining them. I'm not sure what you mean by 14 "the confounding." If -- if a paper has an 15 accounting for confounding? 16 Q (BY MR. ZELLERS) Let me ask you another 17 question. A proper meta-analysis or systematic 18 review must analyze the sources of heterogeneity 19 across the studies; is that right? 20 A Yes. 21 Q And a proper meta-analysis or systematic 22 review must examine the methodology of each of the 23 underlying studies, correct? 24 A Yes. 25 Q You have given some opinions -- or at</p>
<p style="text-align: right;">Page 283</p> <p>1 study; is that right? 2 MS. O'DELL: Object to the form. 3 A Yes, that's definitely possible. 4 Q (BY MR. ZELLERS) Penninkilampi 2018, that 5 study specifically states that a certain causal link 6 between talc use and ovarian cancer has not been 7 established, correct? 8 MS. O'DELL: Object to the form. 9 A I don't remember them concluding that. 10 But if you tell me where -- 11 Q (BY MR. ZELLERS) Sure. 12 A -- it is -- 13 Q Look at page 42, at the end of first 14 paragraph. 15 A Well, perineal talc use has not been shown 16 to be safe. In a similar regard, a certain causal 17 link between the use and ovarian cancer has not been 18 established -- 19 Q And you -- 20 A -- is what -- 21 Q -- okay. 22 A -- Penninkilampi says. 23 Q And I think you omitted the word "talc." 24 But their specific statement is, A certain causal 25 link between talc use and ovarian cancer has not yet</p>	<p style="text-align: right;">Page 285</p> <p>1 least you state some opinions relating to the 2 biological mechanisms of cancer; is that right? 3 A Yes. 4 Q The biological mechanisms of cancer are 5 not your area of expertise; is that correct? 6 MS. O'DELL: Object to the form. 7 A I'm knowledgeable about the biological 8 mechanism of cancer as a scientist, as a physician, 9 as a cancer epidemiologist. 10 Q (BY MR. ZELLERS) Would you agree that 11 there are others who are more closely involved in 12 the area of biologic plausibility as it relates to 13 the perineal use of talcum powder and ovarian 14 cancer? 15 MS. O'DELL: Object to the form. 16 A I believe there are others who have more 17 expertise directly in that area than I do. 18 Q (BY MR. ZELLERS) Your opinion is that 19 talcum powder travels from the perineal region to 20 the ovaries through the women's reproductive tract; 21 is that right? 22 A Yes. 23 Q If talcum powder can make this migration, 24 can other substances make the same migration? 25 A Yes.</p>

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<p>1 Q Sand from the beach?</p> <p>2 A I don't know if there's evidence of sand</p> <p>3 from the beach.</p> <p>4 Q Toilet paper particles?</p> <p>5 A I -- I -- I do not know if there's</p> <p>6 evidence of that.</p> <p>7 Q There are no human studies that</p> <p>8 demonstrate the migration of any particulate matter</p> <p>9 from outside the peri -- peritoneum to the ovaries,</p> <p>10 correct?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A When you say "demonstrate," do you mean</p> <p>13 active demonstration or a suggestion that it has</p> <p>14 gone that route?</p> <p>15 Q (BY MR. ZELLERS) Active -- active</p> <p>16 demonstration.</p> <p>17 A So there are no studies that I know of</p> <p>18 that have taken talcum powder and then documented</p> <p>19 its movement through -- to the ovaries.</p> <p>20 Q Or any particulate from outside the</p> <p>21 perineum to the ovaries, correct?</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 A I -- I don't know of any sort of active</p> <p>24 studies that have watched it moved. It's rather the</p> <p>25 studies have found the particulate matter at its</p>	<p>1 are a lot of other factors such as sphincters or the</p> <p>2 type of mucosa that it is or mucous barriers that</p> <p>3 might have a very strong relationship to the</p> <p>4 concentration of talc.</p> <p>5 So the rectum and the bladder have</p> <p>6 sphincters, and the mucosa and the vagina and the</p> <p>7 bladder and rectum are very different than the</p> <p>8 mucosa of the ovary. The endometrium has different</p> <p>9 tissue.</p> <p>10 So I agree with you that you would expect</p> <p>11 proximity would be one factor that might affect</p> <p>12 concentration. But the characteristics of the</p> <p>13 tissue, the barriers, the physical or mucosal could</p> <p>14 be expected to have a much bigger impact.</p> <p>15 Q No studies that you're aware of show</p> <p>16 inflammation as a result of genital talc use in the</p> <p>17 rectal, vulvar, vaginal, cervical, and uterine</p> <p>18 tissues; is that right?</p> <p>19 A I do not know of those studies.</p> <p>20 Q And no studies show a link between</p> <p>21 external genital talc use and rectal, vulvar,</p> <p>22 vaginal, cervical, or uterine cancer; is that right?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A That is correct.</p> <p>25 Q (BY MR. ZELLERS) You have not done an</p>
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<p>1 destination and then have supposed it had to travel</p> <p>2 there in some way.</p> <p>3 Q (BY MR. ZELLERS) None of the studies that</p> <p>4 you cite in your report actually looked at whether</p> <p>5 talcum powder can migrate from perineal application</p> <p>6 through the fallopian tubes to the ovaries, correct?</p> <p>7 A Correct.</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 Q (BY MR. ZELLERS) You also cannot cite any</p> <p>10 article that shows granulomas, fibrosis, or</p> <p>11 adhesions anywhere up the reproductive tract of a</p> <p>12 women as result of her external genital talc</p> <p>13 application; is -- is that right?</p> <p>14 A Yes.</p> <p>15 Q If talcum powder migrates from the</p> <p>16 perineal region to the ovaries, shouldn't exposure</p> <p>17 to talc be far greater in concentration in the</p> <p>18 rectal, vulvar, vaginal, cervical, and uterine</p> <p>19 tissues which are closer to the area of initial</p> <p>20 exposure?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A I think that assumes that proximity and</p> <p>23 concentration, which you would expect which would</p> <p>24 fall off with more distance, is the only factor that</p> <p>25 would determine concentrations when, in fact, there</p>	<p>1 expert review of the inflammation evidence yourself;</p> <p>2 is that fair?</p> <p>3 MS. O'DELL: Object to the form.</p> <p>4 A I -- I have done a lot of reading of the</p> <p>5 inflammation literature. I'm not sure how I would</p> <p>6 define it as an expert or not an expert -- expert</p> <p>7 review.</p> <p>8 Q (BY MR. ZELLERS) You do know that not all</p> <p>9 inflammatory conditions lead to cancer, correct?</p> <p>10 A There's a lot of literature about certain</p> <p>11 inflammation that causes chronic -- in particular a</p> <p>12 lot of different kind of cancers, more publications</p> <p>13 about acute inflammation that does not lead to</p> <p>14 cancer.</p> <p>15 But yes, there are both cancers that are</p> <p>16 very susceptible to inflammation or caused by it and</p> <p>17 some that are not.</p> <p>18 Q Chronic inflammation. There are many</p> <p>19 chronic inflammatory conditions that do not lead to</p> <p>20 cancer; is that right?</p> <p>21 A Yes.</p> <p>22 Q Do you agree that an agent can be a</p> <p>23 carcinogenic for one type of cancer, but not for</p> <p>24 others?</p> <p>25 A Yes.</p>

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<p>1 Q Rheumatoid arthritis, that is a chronic 2 inflammation condition, but it does not increase the 3 risk of my ovarian cancer, correct? 4 A Correct. 5 Q The same with psoriasis; is that right? 6 A Not that I know of. 7 Q Page 41 of your report, you conclude that, 8 Regular exposure to talcum powder products causes 9 ovarian cancer in some women. 10 Do you see that? 11 A I do. 12 Q Is there a certain amount of talcum powder 13 that a product must contain to cause inflammation? 14 MS. O'DELL: Object to the form. 15 A I -- I -- I do not know of evidence that 16 quantifies the amount of exposure that's necessary 17 that a published literature supports the amount 18 women use is an amount that leads to cancer, but 19 I -- I don't know if there's a minimum threshold 20 or... 21 Q (BY MR. ZELLERS) Do you consider 22 cornstarch to be a talcum powder product that causes 23 inflammation? 24 MS. O'DELL: Object to the form. 25 A Talcum powder -- cornstarch -- talcum</p>	<p>1 A In a few of the papers I reviewed -- not 2 very many of them, but a few of them had a small 3 proportion of women who were exposed to cornstarch 4 rather than talc powder products. 5 I -- I think it -- they had negative 6 results, but they were small -- a small number of 7 women, so I wouldn't use that to prove that it's 8 safe. 9 But I don't know of any literature that 10 suggests cornstarch is carcinogenic. 11 Q Your opinion that talcum powder products 12 cause inflammation is not based on the determination 13 that there is a threshold amount of talcum powder 14 that will be required to be in the product before 15 you can conclude that the product will cause chronic 16 inflammation; is -- is that right? 17 MS. O'DELL: Object to the form. 18 A I -- I -- I think I would like to agree. 19 I'm just not sure exactly of -- what I am agreeing 20 to. So I -- I don't know any level -- 21 MS. O'DELL: That's always -- 22 A -- of -- 23 MS. O'DELL: -- a good sign you should -- 24 A -- I -- I can't -- 25 MS. O'DELL: -- be --</p>
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<p>1 powder causes inflammation. Cornstarch can also 2 cause inflammation. 3 I believe cornstarch tends to be an acute 4 inflammatory process rather than a chronic 5 inflammation process. But -- 6 Q (BY MR. ZELLERS) You -- 7 A -- I -- I wouldn't consider cornstarch to 8 be a talcum powder -- 9 Q Is -- 10 A -- product. 11 Q -- is there a study that you can point me 12 to that states that any inflammation from cornstarch 13 is acute and not chronic? 14 MS. O'DELL: Object to the form. 15 A There's a literature about cornstarch 16 leading to acute inflammation, for example, in the 17 surgical literature when it was on surgical gloves 18 or on physical exams which has led to its being 19 removed so -- so as to reproduce acute inflammatory 20 processes. 21 Q (BY MR. ZELLERS) My question to you is: 22 Are you aware of any literature that states that 23 cornstarch is not associated with a chronic 24 inflammatory condition? 25 MS. O'DELL: Object to the form.</p>	<p>1 A -- I can't tell exactly what the -- what 2 the question is. 3 I -- there -- I don't know -- I don't know 4 an amount of talcum powder that would make a product 5 safe. 6 Q (BY MR. ZELLERS) Do you believe that 7 cornstarch is a superior alternative to talc? 8 A I believe that talcum powder products will 9 increase women's risk of cancer, and I would avoid 10 using it as a woman or as a doctor counseling my 11 patients. 12 Q Well -- 13 A I don't have views that cornstarch is a 14 carcinogenic product. So in terms of any potential 15 risk-benefit relationship of cornstarch has the same 16 value in terms of absorbency and much fewer risk of 17 harm, then if that's the question, then I think 18 cornstarch is preferable. 19 Q There are no reports in the literature of 20 externally applied talc leading to inflammation, 21 granulomas, fibrosis, or adhesions anywhere along a 22 women's reproductive tract, correct? 23 MS. O'DELL: Objection, asked and 24 answered. 25 A Not that I know of.</p>

13 (Pages 290 to 293)

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<p style="text-align: right;">Page 294</p> <p>1 Q (BY MR. ZELLERS) On page 12 of your report 2 you state, The most widely accepted mechanism for 3 initiation, promotion, and progression of ovarian 4 cancer is tissue inflammation, leading to a series 5 of responses that result in cancer. 6 Do you see that statement? 7 A I do. 8 Q You do not cite any support in your report 9 for that proposition, correct? 10 MS. O'DELL: Object to the form. 11 A I -- I think my -- that first paragraph 12 was sort of an introduction to that section. So 13 then I go on to cite, I -- I think, the supporting 14 evidence within the next few paragraphs. 15 Q (BY MR. ZELLERS) You would agree that 16 research regarding whether chronic inflammation can 17 cause ovarian cancer is ongoing, correct? 18 A It's an active area of research. 19 Q Are you familiar with a paper published by 20 Melissa Merritt in 2008, entitled "Talcum Powder 21 Chronic Pelvic Inflammation and NSAIDS in Relation 22 to Risk of Epithelial Ovarian Cancer"? 23 A I am. 24 Q It's included in your reliance materials 25 on page 17; is that right?</p>	<p style="text-align: right;">Page 296</p> <p>1 inflammation; is that right? 2 A Yes, they do. 3 Q If inflammation is a mechanism for ovarian 4 cancer, you would expect women who use NSAIDS or 5 aspirin to have a lower risk of ovarian cancer, 6 correct? 7 MS. O'DELL: Object to the form. 8 A Other things being equal, you might expect 9 that if you could measure inflammation or influence 10 it by using NSAIDS, that that might be associated. 11 That is true. 12 Q (BY MR. ZELLERS) The literature, though, 13 is mixed in terms of whether or not the use of 14 NSAIDS or aspirin actually reduce the risk of 15 ovarian cancer; is that right, or the incidence of 16 -- 17 A So -- 18 Q -- ovarian cancer? 19 A -- I have reviewed those papers and would 20 agree with you that some seem to suggest one 21 direction, some others. I haven't quantified them 22 together or tried to summarize them. 23 But I would agree. There doesn't seem to 24 be a consistent message in that literature. 25 Q One of those papers is -- that's included</p>
<p style="text-align: right;">Page 295</p> <p>1 A Can you tell me the title again? Yeah. 2 Okay. 3 Q Sure. Do you have that or I can -- 4 A No. 5 Q -- mark it? 6 A No, I have it. 7 Q If you go to page 174 of the Merritt 8 paper -- and tell me when you're -- 9 A I'm there. 10 Q -- there -- at the bottom of the first 11 paragraph of the discussion, the authors conclude, 12 These results, in combination with previous studies, 13 suggest that chronic inflammation is unlikely to 14 play a major role in the development of ovarian 15 cancer. 16 Is that right? Did I read that correctly? 17 A Using the results that they had available 18 on the data in 2007, that is what Dr. Merritt 19 concluded. 20 Q You also discuss in your report -- well, 21 let me withdraw that. 22 You're familiar with NSAIDS, nonsteroidal 23 antiinflammatory agents; is that right -- 24 A Yes, I am. 25 Q -- and aspirin? Those medicines reduce</p>	<p style="text-align: right;">Page 297</p> <p>1 in your reliance list is the Verdoodt 2017 paper; is 2 that right? That's V E R D O O D T. 3 A I am going to have to defer to seeing 4 that. 5 Q Okay. Let me -- 6 A I believe -- 7 Q -- show you -- 8 A -- it's on my list. 9 Q -- I will mark that paper as Exhibit 31. 10 (Exhibit 31 was marked for identification 11 and is attached to the transcript.) 12 A Thank you. 13 Q (BY MR. ZELLERS) And turn, if you will, to 14 page 5 under "Discussion" on the first paragraph. 15 A And just to confirm, this is -- I -- I 16 have read this. This is a review article, right? 17 Q Yes. 18 A Okay. 19 Q So on page 5 under "Discussion," the first 20 sentence, the authors state, The sparse and 21 equivocal results for the association between NSAID 22 use and mortality among ovarian and endometrial 23 cancer patients preclude any firm conclusions at 24 this point. 25 Is that right?</p>

14 (Pages 294 to 297)

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<p>1 A That is what this author concludes. I'm 2 trying to see what references he used for that, but 3 that is what he concludes. 4 Q Okay. And this is an article that was 5 published in 2017, correct? 6 A Yes. 7 Q Yesterday counsel for plaintiffs indicated 8 that you have -- in addition to the materials in 9 your report -- reviewed a 2018 chapter by Saed and 10 the Harper and Saed 2019 abstract; is that right? 11 A I -- I reviewed several of his abstracts 12 and -- and a recent paper, yes. 13 Q Do you know that Dr. Saed is a paid expert 14 for the Plaintiffs in this litigation? 15 A I know he's a very well-respected 16 scientist that they have supported in his research. 17 Q Is that a yes? 18 MS. BOCKUS: I object. Nonresponsive. 19 MS. O'DELL: Mike, excuse me. 20 MR. ZELLERS: Sure. 21 MS. O'DELL: You said the 2019 abstract. 22 Did you mean the abstract or the manuscript, just to 23 make sure I'm following the conversation? 24 MR. ZELLERS: I -- I believe I mean the 25 abstract. But we mean whatever the doctor has in</p>	<p>1 Q Have you spoken with Dr. Saed? 2 A I have not. 3 Q Have you requested any information from 4 Dr. Saed? 5 A I have not. 6 Q The Saed study just looked at immortalized 7 cell lines; is that right? 8 A Yes, I believe that's how the cell lines 9 were -- 10 Q Are -- 11 A -- defined. 12 Q -- are you -- are you aware that Dr. Saed 13 testified that the cells were modified with a virus 14 to make them keep undergoing division in vitro? 15 A I -- I'm aware that that's what happens to 16 cell lines. I -- I don't believe I saw his 17 deposition to say that. 18 Q Are you aware that Dr. Saed testified that 19 the P53 gene was turned off in those cells? 20 A No, I'm not aware. 21 Q Are you aware based upon your reading that 22 the loss of the P53 protein contributes to 23 unrestrained cellular proliferation? 24 MS. O'DELL: Object to the form. 25 A I -- I believe that the reason you have</p>
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<p>1 her file that we marked yesterday. 2 THE COURT REPORTER: Who objected down 3 there? 4 MS. BOCKUS: Jane Bockus. 5 MS. O'DELL: I think what she had in her 6 file was the manuscript. So I think that's what you 7 marked as an exhibit, but I don't want there to be 8 confusion. 9 Q (BY MR. ZELLERS) You have reviewed several 10 publications within the last year or two from 11 Dr. Saed -- 12 A Yes. 13 Q -- is that right? 14 A Yes, I have. 15 THE COURT REPORTER: Wait. 16 MR. ZELLERS: All right. Are you okay, 17 Ms. Court Reporter? 18 THE COURT REPORTER: Yes. I just have to 19 have you wait until the end of the question, please. 20 Q (BY MR. ZELLERS) Let me re-ask my -- 21 A Please. 22 Q -- question. Did you know that Dr. Saed 23 is a paid expert for the Plaintiffs in this 24 litigation? 25 A Yes, I do.</p>	<p>1 controls in experiment is to account for the 2 underlying expression in turnover cells so you can 3 compare something you do to the cell versus the 4 baseline in order to account for the baseline, 5 whatever it is, proliferation of the cell or 6 apoptosis levels or expression of oxidants or 7 antioxidants. 8 So I -- I -- the way you're asking the 9 question is -- is: Are you comparing this cell line 10 to living cells in context? 11 And I would agree with you that this cell 12 line is different than living cells in context. 13 But if you're asking if it's a valid 14 comparison to do the experiment in this cell line, 15 it is because you are doing an intervention to those 16 cells that has a control group. 17 And so this cell line has a different 18 behavior than a -- a living cell does, but provides 19 a comparison group. 20 Q (BY MR. ZELLERS) What methodology did you 21 use to apply Dr. Saed's results to normal cells in 22 actual organs? 23 A So -- 24 MS. O'DELL: Object to the form. 25 A -- in some of the work that I do around a</p>

15 (Pages 298 to 301)



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<p>1 different environmental carcinogen -- radiation, for 2 example -- we look at changes of expression, certain 3 enzymes in cells to radiation to understand what 4 that damage does in terms of expression of relevant 5 genes, cell proliferation, and things like that. 6 So I take his research to mean that I can 7 understand the changes to pro oxidants to 8 antioxidants to apoptosis to gene expression in the 9 cell. Not that I can come up with the exact 10 quantification in a patient that would correspond to 11 it, but rather, what mechanisms will be stimulated 12 by the talc. 13 So to answer your question, I -- it tells 14 me what parts of the cell are sensitive to it, but 15 not the quantity that might lead to that 16 sensitivity. 17 Q (BY MR. ZELLERS) Can you cite any data 18 showing that the concentrations of exposure used in 19 the Saed study are the same as would be encountered 20 with the use of cosmetic talc in the perineal 21 region? 22 A I cannot. That's what I was trying to 23 express. 24 Q Can you cite any data showing that the 25 level of concentration of exposure used in the Saed</p>	<p>1 develop enough mutations to develop into cancer. 2 But the greater the oxidative stress for 3 cancer like ovarian cancer, the greater the chance 4 of inducing cancer. 5 Q Can you cite me to any study that says 6 that? 7 MS. O'DELL: Object to the form. 8 A Any study that says that there's a dose 9 response related to the amount of stress and the 10 member -- numbers of cancers? 11 Q (BY MR. ZELLERS) That supports, yes, your 12 statement and your position. 13 A I -- the data that I am thinking of -- and 14 I'm not sure if it's quite the same as the question 15 that you're asking -- is the number of gene 16 mutations is higher in cancer cells than it is in 17 noncancer cells. So -- 18 THE COURT REPORTER: In noncancer? 19 A In non -- cancer cells have many more 20 genetic mutations than noncancer cells. 21 Both have generic mutations. And the 22 environment of having more oxidative stress is 23 associated with getting more mutations -- 24 Q (BY MR. ZELLERS) If -- if it's -- 25 A -- but --</p>
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<p>1 study has ever occurred in women with perineal talc 2 use? 3 MS. O'DELL: Object to the form. 4 A I want to clarify my answer. I don't know 5 those data. 6 Q (BY MR. ZELLERS) Would you agree that 7 reactive oxygen species are a normal part of cell 8 physiology? 9 A Yes. 10 Q Do all substances that cause oxidative 11 stress also cause cancer? 12 A I think you care about the balance of 13 oxidative, pro oxidative, antioxidative levels. 14 That being said, I do not know that every 15 instance where you have more pro oxidative leads to 16 cancer. I know of some where it does. I don't know 17 if it always does. 18 Q Does the presence of oxidative stress in a 19 tissue indicate that cancer will develop in that 20 tissue? 21 A I think I mentioned this yesterday, that 22 there's a sense of a probability. So the 23 probability will likely increase. 24 But most cells, thankfully, will repair 25 and -- that damage, and so most cells will not</p>	<p>1 Q -- are you finished? 2 A -- I -- I am. 3 Q Okay. If -- if exposure to a substance 4 causes oxidative stress in certain tissue, does that 5 mean that the substance will cause oxidative stress 6 in all types of tissues? 7 A No. 8 Q Does the body have a protective mechanism 9 that can limit tissue damage from oxidative stress? 10 A Yes. 11 Q Are there any publications that you are 12 aware of that indicate that oxidative stress is 13 involved in the development of ovarian cancer? 14 A We discussed earlier that inflammation 15 increases oxidative stress such as pelvic 16 inflammatory disease leads to oxidative stress. 17 And pelvic inflammatory disease is 18 associated and leads to ovarian cancer. But I'm not 19 sure if that's answers the question that you are... 20 Q Well, if I had more time, we would discuss 21 that at greater length. You're familiar with the 22 term "confounding" is that right? 23 A I -- I -- Yes, I'm -- 24 Q All right. 25 A -- familiar with that term.</p>



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<p style="text-align: right;">Page 306</p> <p>1 Q Confounding is where the presence of</p> <p>2 another association confuses the relationship</p> <p>3 between the exposure and the disease being studied;</p> <p>4 is -- is that right?</p> <p>5 A Yes.</p> <p>6 Q Confounding can distort results in</p> <p>7 epidemiological studies; is that right?</p> <p>8 A Yes.</p> <p>9 Q Would you agree that residual confounding</p> <p>10 is possible in every observational study?</p> <p>11 A Yes.</p> <p>12 Q It's also -- strike that.</p> <p>13 It's possible that unmeasured confounders</p> <p>14 may be present in every observational study,</p> <p>15 correct?</p> <p>16 A Yes.</p> <p>17 Q It's impossible to say that all known and</p> <p>18 unknown confounding factors have been controlled for</p> <p>19 in any given study; is that right?</p> <p>20 A Yes.</p> <p>21 Q Would you agree that there are new factors</p> <p>22 that are being discussed that are possibly involved</p> <p>23 with ovarian cancer that are just being published in</p> <p>24 the literature such as a history of chlamydia</p> <p>25 infection and a history of weight gain during</p>	<p style="text-align: right;">Page 308</p> <p>1 is unavoidable in this type of summary. The large</p> <p>2 difference in general between adjusted and crude</p> <p>3 results emphasizes the importance of adjustments</p> <p>4 when estimating particular risk?</p> <p>5 THE COURT REPORTER: When estimating?</p> <p>6 MR. ZELLERS: Particular risk.</p> <p>7 A Are you asking what I meant by that?</p> <p>8 Q (BY MR. ZELLERS) Yes. What did you mean</p> <p>9 by that?</p> <p>10 A Okay. I -- I would say my sentence is not</p> <p>11 as clear as it should have been. What I mean -- and</p> <p>12 I'm not really sure why I pointed this out just for</p> <p>13 Berge -- it's really a general -- is that the</p> <p>14 studies they included, adjusted for different</p> <p>15 covariates.</p> <p>16 They didn't all adjust for the same</p> <p>17 covariates. So a variety of covariates, meaning</p> <p>18 they didn't all adjust for the exact same</p> <p>19 covariates.</p> <p>20 But this is unavoidable in this type of</p> <p>21 study. So I was just saying that some of the</p> <p>22 included studies adjusted for A, B and C; and others</p> <p>23 were adjusted for B, C, and D; and others D, E, and</p> <p>24 F.</p> <p>25 Q Huncharek, page 26. Do you see that</p>
<p style="text-align: right;">Page 307</p> <p>1 adolescence?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A Chlamydia infection would be the most</p> <p>4 common infection of PID, and so that's something</p> <p>5 that I just mentioned. I'm not sure that that's</p> <p>6 such a new one.</p> <p>7 And weight gain during adolescence is</p> <p>8 something that's of interest across a range of</p> <p>9 cancers, like breast cancer. I don't know it</p> <p>10 personally around ovarian cancer, but...</p> <p>11 Q (BY MR. ZELLERS) Those factors that we</p> <p>12 just talked about generally have not been controlled</p> <p>13 for in any of the published talcum powder ovarian</p> <p>14 cancer studies; is that right?</p> <p>15 A I -- the PID, I -- I think, has it in a</p> <p>16 paper or two. And -- and the weight gain, I -- I</p> <p>17 don't -- I have never seen that one.</p> <p>18 Q We talked yesterday about the Berge study.</p> <p>19 Do you remember that?</p> <p>20 A I do.</p> <p>21 Q And you talk about Berge on page 25 of</p> <p>22 your report.</p> <p>23 What do you mean when you say, A second</p> <p>24 limitation of Berge is that the included studies</p> <p>25 adjusted for a variety of covariates, although this</p>	<p style="text-align: right;">Page 309</p> <p>1 reference where you talk about that study?</p> <p>2 A Yes.</p> <p>3 Q You say that the difference between a</p> <p>4 relative risk of 1.19 and 1.38 is small; is that</p> <p>5 right?</p> <p>6 MS. O'DELL: You're talking about 2007 or</p> <p>7 2003?</p> <p>8 Q (BY MR. ZELLERS) Whichever --</p> <p>9 A Which page?</p> <p>10 Q -- so page 26 --</p> <p>11 MS. O'DELL: They're both on the same</p> <p>12 page.</p> <p>13 Q (BY MR. ZELLERS) I think I'm looking at</p> <p>14 the one at the bottom.</p> <p>15 MS. O'DELL: Okay. All right. 2003?</p> <p>16 MR. ZELLERS: Yes.</p> <p>17 Q (BY MR. ZELLERS) So are you with me? Are</p> <p>18 you looking at your last couple of lines there on</p> <p>19 page 26?</p> <p>20 A Yes.</p> <p>21 Q And you do say that the difference between</p> <p>22 a relative risk of 1.19 and 1.38 is small; is that</p> <p>23 right?</p> <p>24 A It -- odds ratios --</p> <p>25 Q Yeah.</p>

17 (Pages 306 to 309)

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<p>1 A -- but yes.</p> <p>2 Q All right. And -- and so a difference in</p> <p>3 odds ratios of .19, you would consider that to be a</p> <p>4 small difference?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A You're asking why I said those differences</p> <p>7 are small?</p> <p>8 Q (BY MR. ZELLERS) No. Well, what I guess</p> <p>9 what I want to know is: Would you agree that the</p> <p>10 difference between an odds ratio of 1.0 and 1.2 is</p> <p>11 small?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A I think the question of whether or not you</p> <p>14 have a difference of absolute odds of .2 along</p> <p>15 different values means the same thing. And I would</p> <p>16 say it doesn't mean the same thing.</p> <p>17 So if you have an odds ratio as an example</p> <p>18 of 4.7 versus 4.9, they're kind of the same number.</p> <p>19 If you have a number that's 1.0 versus 1.2, those</p> <p>20 are not the same number.</p> <p>21 So I don't think you would want to assume</p> <p>22 the shift in the absolute magnitude of the</p> <p>23 difference in odds. I often published difference in</p> <p>24 odds ratios of .2 is stable.</p> <p>25 But I think is -- your point is well taken</p>	<p>1 A Yeah.</p> <p>2 Q -- yesterday?</p> <p>3 A So the most important -- as it points out</p> <p>4 here in -- in Huncharek, the next sentence of where</p> <p>5 we are, is that this review looked at any exposure</p> <p>6 rather than quantifying.</p> <p>7 And I think the primary concern that I had</p> <p>8 was that any exposure is a very vague definition.</p> <p>9 And I thought it was much more important to have a</p> <p>10 meaningful measure of exposure.</p> <p>11 So the studies that I primarily included</p> <p>12 were ones that had quantification of the exposure,</p> <p>13 but also had some other requirements.</p> <p>14 I -- I -- I want to say that my systematic</p> <p>15 review was one piece of the information that I</p> <p>16 considered, but my summary estimate in the</p> <p>17 systematic review that I completed had the same</p> <p>18 conclusion as all these other systematic reviews.</p> <p>19 In the ballpark, it just gave me greater</p> <p>20 confidence that we were truly looking at regular</p> <p>21 exposure rather than any exposure.</p> <p>22 Now, we know that the most common exposure</p> <p>23 is regular exposure. That's the -- the more</p> <p>24 important -- most common.</p> <p>25 Q Take a look at page 39 in your report</p>
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<p>1 that that's not a trivial difference. I was just</p> <p>2 saying in the context of a systematic review, those</p> <p>3 are both very strong, positive associations, and</p> <p>4 that's a relatively minor difference.</p> <p>5 Q (BY MR. ZELLERS) An odds ratio range of</p> <p>6 1.19 to 1.38 is much closer to an odds ratio of 1.0</p> <p>7 to 1.2 than it is to an odds ratio of 4.5 to 4.7,</p> <p>8 correct?</p> <p>9 A I -- I think that's a valid -- a valid</p> <p>10 comparison.</p> <p>11 Q On page 26, 27, there's a carryover there,</p> <p>12 but you state that the population controls are more</p> <p>13 likely relevant and valid than hospital controls.</p> <p>14 What's your support for that?</p> <p>15 A It's what we discussed earlier. I -- I</p> <p>16 think population-based controls are -- are better</p> <p>17 than hospital-based controls.</p> <p>18 Q With respect to your systematic review,</p> <p>19 did you attempt to identify gaps or flaws in the</p> <p>20 underlying studies?</p> <p>21 A I reviewed the individual studies and set</p> <p>22 forth criteria that I thought were required for</p> <p>23 inclusion.</p> <p>24 Q What were those criteria? Are those</p> <p>25 contained in your forms that we talked about --</p>	<p>1 where you discuss temporality; is that right?</p> <p>2 A Yes.</p> <p>3 Q You say that women may use talc when</p> <p>4 undergoing ovarian cancer treatment.</p> <p>5 Do you see that?</p> <p>6 A Yes.</p> <p>7 Q What is your support for that or what is</p> <p>8 that statement based on?</p> <p>9 A I -- I think it's based on my clinical</p> <p>10 experience that postop patients often will use</p> <p>11 talcum powder products for systematic relief of</p> <p>12 symptoms that could be related to the surgical</p> <p>13 procedure itself.</p> <p>14 Q All right. Asbestos. Are your opinions</p> <p>15 in this case dependent on talcum powder containing</p> <p>16 asbestos?</p> <p>17 A No, they're not.</p> <p>18 Q Are your opinions in this case dependent</p> <p>19 on talcum powder containing trace amounts of metals?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A No, they're not.</p> <p>22 Q (BY MR. ZELLERS) Are your opinions in this</p> <p>23 case dependent upon talcum powder containing any</p> <p>24 particular fragrance chemical?</p> <p>25 A No, they're not.</p>

18 (Pages 310 to 313)

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<p>1 Q Do you believe that talcum powder, which 2 does not contain asbestos, causes ovarian cancer? 3 A I don't have any data on which to conclude 4 based on epidemiologic evidence that there is such a 5 product, so I don't know that there is any product 6 that has been studied that doesn't contain asbestos 7 and fibrous talc. 8 I think in a laboratory setting, people 9 have studied products that they describe as being 10 asbestos free, and those products do cause cellular 11 damage. 12 But from an epidemiologic perspective, 13 which is primarily the data I looked at, all of the 14 products that have been studied, I believe contain 15 asbestos and fibrous talc. 16 Q You have made an assumption or it is your 17 belief that all talcum powder products contain 18 asbestos; is that right? 19 MS. O'DELL: Object to the form. 20 A My belief is that many talcum powder 21 products contain asbestos or -- 22 Q (BY MR. ZELLERS) If -- 23 A -- fibrous. 24 Q -- if your assumption about contamination 25 of talcum powder products with asbestos were not</p>	<p>1 A I -- I haven't seen any. 2 Q (BY MR. ZELLERS) Have you requested any? 3 MS. O'DELL: Object to the form. There 4 have been no defense expert reports in this case. 5 MR. ZELLERS: Counsel, please object to 6 form. There have been many defense expert reports 7 in the talcum powder litigation generally. 8 But my question was whether or not she has 9 seen anything, so she can -- I think she has already 10 answered. 11 Q (BY MR. ZELLERS) Is that right? Have you 12 answered the question? 13 MS. O'DELL: Object to the form. 14 A I have asked to see reports. No. I have 15 asked to see testing results. I have not asked to 16 see reports. 17 Q (BY MR. ZELLERS) Have you seen testing 18 results from the FDA and its testing of talcum 19 powder? 20 A I have. 21 Q The FDA did some testing in 2010. Did you 22 see those results? 23 A I did. 24 MS. O'DELL: Do you need a break or are 25 you good or --</p>
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<p>1 true, would that change your opinions in this case? 2 MS. O'DELL: Object to the form. 3 A In -- in this case, it would not. I -- 4 I -- the epidemiologic evidence is very strong that 5 exposure to talcum powder products, whatever it 6 contains, is carcinogenic. 7 Q (BY MR. ZELLERS) You have looked at 8 several reports from Dr. Longo; is that right? 9 A I have. 10 Q You're aware he is a paid litigation 11 expert; is that right? 12 A Yes, I am. 13 Q You're aware he wrote his reports for the 14 purpose of this litigation and that those reports 15 have not been published; is that right? 16 A I -- I know that he has generated a report 17 for this, yes. 18 Q Do you know if any defense ex -- strike 19 that. 20 Do you know if any defense experts have 21 addressed or responded to Dr. Longo's litigation 22 reports? 23 MS. O'DELL: I would object to the form. 24 There's been no defense reports in this case, as you 25 know.</p>	<p>1 A I actually would love a -- a break. I 2 don't mind going a few more minutes, if that would 3 be good or -- but otherwise, I would love a break. 4 MS. O'DELL: Whenever is a good time. 5 MR. ZELLERS: Sure. I'll just finish 6 this. 7 Q (BY MR. ZELLERS) I'll hand you the 8 exhibit, Exhibit 32. 9 (Exhibit 32 was marked for identification 10 and is attached to the transcript.) 11 Q (BY MR. ZELLERS) Is that -- 12 A Thank you. 13 Q -- the -- at least some of the testing by 14 the FDA that you have seen? 15 A Yes, it is. 16 Q That testing was done by an independent 17 laboratory; is that right? 18 A I -- I -- I don't know that, but I believe 19 you. 20 Q Take -- 21 MS. O'DELL: Do you have a copy for me? 22 MR. ZELLERS: Oh, I'm so sorry. I have 23 that, yes. Sorry. 24 MS. O'DELL: Thanks. 25 Q (BY MR. ZELLERS) If you go to the second</p>

19 (Pages 314 to 317)

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<p>1 page, the second paragraph, We contracted with AMA 2 Analytical Services of Lanham, Maryland, to conduct 3 this laboratory service -- or strike that -- survey. 4 Do you see that? 5 A I don't. I'm on the right page. 6 Q On the second page. 7 A The second page. 8 Q The second paragraph, the second -- 9 A Yes. 10 Q -- sentence -- 11 A -- yes. Yes. Thank you. 12 Q All right. 13 A Yes. 14 Q And at least based upon this report, no 15 asbestos was detected in the talcum powder that was 16 tested; is that right? 17 A In the reports that they show, which 18 might -- my understanding is that they had two 19 samples of baby powder, talcum powder in this. And 20 that in those two specimens using the testing method 21 they used, they didn't find evidence of asbestos. 22 MR. ZELLERS: All right. Let's take a 23 break. 24 THE VIDEOGRAPHER: The time is 10:47 a.m. 25 We are now off the record.</p>	<p>1 would like -- she edits all of my publications 2 before I submit them. 3 Q (BY MR. ZELLERS) When we left the last 4 session, I asked you about asbestos and whether or 5 not asbestos is contained in talcum powder. 6 Is there any amount of asbestos that would 7 be safe in talcum powder products? 8 A And the simple answer would be no, I don't 9 think there's any amount that would be safe in 10 talcum powder products. 11 Q All right. Is there any amount of trace 12 metals that would be safe in talcum powder products? 13 MS. O'DELL: Object to the form. 14 A I believe there would be amounts of trace 15 metals that would be acceptable. 16 Q (BY MR. ZELLERS) Are there any amounts of 17 fragrance chemicals that would be safe in talcum 18 powder products? 19 A I believe there would be in certain 20 categories. And in others, there would not. 21 Q There have been no fragrance chemicals, to 22 your knowledge, that have been found in a study to 23 be associated with ovarian cancer, correct? 24 MS. O'DELL: Object to the form. 25 A I -- I know of no -- no such exploration.</p>
Page 319	Page 321
<p>1 (A break was taken from 10:47 a.m. to 1 2 11:00.) 3 THE VIDEOGRAPHER: It's 11:00 a.m. We are 4 now back on the record. Here begins Media No. 2 of 5 the deposition of Dr. Rebecca Smith-Bindman, Ph.D., 6 Volume II. 7 Q (BY MR. ZELLERS) Dr. Smith-Bindman, I was 8 handed the invoice for Chris Tachibana, which we 9 have marked as Exhibit 33. 10 (Exhibit 33 was marked for identification 11 and is attached to the transcript.) 12 Q (BY MR. ZELLERS) Is that the invoice that 13 your copy editor provided to you? 14 A Yes. 15 Q Are there any other invoices that you have 16 received from her? 17 A No. 18 Q Do you expect there to be any other work 19 that Ms. Tachibana does with respect to your report? 20 A Not with respect to my report. 21 If I move ahead to publish these results, 22 then I would likely reach out to her to help -- as 23 well. 24 THE COURT REPORTER: To help? 25 A If we choose to publish the results, I</p>	<p>1 Q (BY MR. ZELLERS) Do you have an opinion on 2 what type of asbestos is in talcum powder products? 3 A I believe asbestos is sort of a family of 4 chemicals. I think there are six that kind of get 5 grouped together. I think all of them have been 6 identified in talcum powder products, but I don't 7 know the distribution of the different kinds. 8 Q What type of asbestos is associated with 9 ovarian cancer? And by that question, you believe 10 that there's six subtypes of asbestos -- 11 MS. O'DELL: Object to the form. 12 Q (BY MR. ZELLERS) -- is that generally your 13 understanding? 14 A It's generally my understanding. 15 Q Are -- are you able to give us any 16 opinions with respect to what type or types of 17 asbestos is associated with ovarian cancer? 18 A The -- the strongest summary of the 19 relationship that I know about is in the IARC 2012 20 reports. 21 And those are from a number of different 22 studies, including some cohort studies and case 23 control studies. 24 To my knowledge, I don't know that they 25 have divided them by the type of mineral silicate</p>

20 (Pages 318 to 321)

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<p>1 fibers that were in those studies.</p> <p>2 Q What amount of asbestos exposure is</p> <p>3 associated with ovarian cancer?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A To the best of my knowledge, the amount</p> <p>6 that's contained within talc powder products is</p> <p>7 probably associated with -- the amount that's in</p> <p>8 there is probably the -- cancer.</p> <p>9 Q (BY MR. ZELLERS) Can you be any more</p> <p>10 definitive?</p> <p>11 A The talcum powder products that women have</p> <p>12 used is associated with ovarian cancer. And I</p> <p>13 believe that to know how much asbestos it takes to</p> <p>14 cause cancer, the easiest way to answer that is to</p> <p>15 quantify how much asbestos is within the --</p> <p>16 the powder products.</p> <p>17 So I'm not in any way an expert on this.</p> <p>18 But in the Longo report, it talked about an average</p> <p>19 of 50,000 particles of asbestos being in each</p> <p>20 gram of -- on average in each gram of baby powder</p> <p>21 products.</p> <p>22 And he estimates that in a container, that</p> <p>23 would be millions of particles, which seems like a</p> <p>24 large number to me, but -- so I don't know the</p> <p>25 amount that would be required to be carcinogenic,</p>	<p>1 A I did not.</p> <p>2 Q Would you agree that research on the</p> <p>3 potential relationship between asbestos and ovarian</p> <p>4 cancer has only considered a small number of cases?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A I think the IARC review on the</p> <p>7 occupational exposures to asbestos had quite a</p> <p>8 number of cancers, but I would have to go back to</p> <p>9 those studies to remember the number.</p> <p>10 Q (BY MR. ZELLERS) Did you review the Reid</p> <p>11 2011 study?</p> <p>12 A I believe that's one that I -- I reviewed.</p> <p>13 Q Do you need me to hand that to you if --</p> <p>14 A Yes --</p> <p>15 Q -- ask you a couple of questions about it?</p> <p>16 A -- please.</p> <p>17 Q Now, in the Reid 2011 paper, which we will</p> <p>18 mark as Exhibit 34 --</p> <p>19 A And is that one of the studies that</p> <p>20 Camargo included in -- I think it is -- in his</p> <p>21 systematic review? Yeah. So this is a different</p> <p>22 systematic review.</p> <p>23 (Exhibit 34 was marked for identification</p> <p>24 and is attached to the transcript.)</p> <p>25 Q (BY MR. ZELLERS) Do you recognize</p>
Page 323	Page 325
<p>1 but that's the amount that they were exposed to that</p> <p>2 was carcinogenic.</p> <p>3 Q What type of ovarian cancer is asbestos</p> <p>4 associated with?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A I think the most stable estimate of the</p> <p>7 association of talcum powder products with ovarian</p> <p>8 cancer is for all ovarian cancer and the</p> <p>9 meta-analysis that others did. And my summary</p> <p>10 estimate was for all ovarian cancer -- epithelial</p> <p>11 ovarian cancer, I should say.</p> <p>12 In my more limited review, I focused on</p> <p>13 serous cancer, because I think as the most common</p> <p>14 cancer -- the most common invasive cancer, it's the</p> <p>15 one where there's enough statistical power to</p> <p>16 quantify the association, so I think the data are</p> <p>17 the most compelling for serous ovarian cancer.</p> <p>18 But the overall meta-analysis looks at any</p> <p>19 cancer, and that's what we did as well.</p> <p>20 Q You -- you looked at talcum powder,</p> <p>21 correct?</p> <p>22 A Talcum powder products, yes.</p> <p>23 Q You did not undertake a Bradford Hill</p> <p>24 analysis of the literature on asbestos and ovarian</p> <p>25 cancer, correct?</p>	<p>1 Exhibit 34?</p> <p>2 A No.</p> <p>3 Q Okay. Well, Exhibit 34 is a study and --</p> <p>4 and a review by the first named author, Allison</p> <p>5 Reid.</p> <p>6 "Does Exposure to Asbestos Cause Ovarian</p> <p>7 Cancer?"</p> <p>8 A I -- I have seen this paper.</p> <p>9 Q All right.</p> <p>10 A I'm sorry. I didn't remember. So sorry.</p> <p>11 Q If you look at her conclusions -- or the</p> <p>12 author's conclusions on the right-hand side of the</p> <p>13 first page -- so I'm --</p> <p>14 A Yes.</p> <p>15 Q -- looking right here --</p> <p>16 A Yes.</p> <p>17 Q -- the relationship between asbestos</p> <p>18 exposure and ovarian cancer is not well</p> <p>19 understood -- is not as well understood as -- as</p> <p>20 that of asbestos-related diseases. Studies that</p> <p>21 have examined this issue have been limited for two</p> <p>22 major reasons.</p> <p>23 No. 1, there's a small number of cases.</p> <p>24 And No. 2, there's difficulties with diagnosis and</p> <p>25 specifically distinguishing between peritoneal</p>

21 (Pages 322 to 325)



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<p>1 mesothelioma and ovarian cancer; is -- is that 2 right? 3 MS. O'DELL: Object to the form. 4 A So this -- those are the conclusions that 5 she makes. But I -- I want just to explain what she 6 means by "small number of cases." 7 She's comparing it to the number of men 8 exposed to asbestos. Just there -- there are many 9 more men exposed to asbestos than -- than women 10 exposed to asbestos. 11 So I think -- I mean, I -- I think it's a 12 challenge, but I -- wouldn't say that there are a 13 small number of cases. 14 MR. ZELLERS: Move to strike as 15 nonresponsive. 16 Q (BY MR. ZELLERS) Would you agree that most 17 of the studies that have been done and the data that 18 exists relates to occupational exposure of asbestos 19 and ovarian cancer? 20 A Yes. I -- 21 Q All right. 22 A -- yes. 23 Q You looked at the Camargo paper 2011; is 24 that right? 25 A Yes.</p>	<p>1 author state, Further limitation of our analysis was 2 its inability to account for nonoccupational risk 3 factors for ovarian cancer other than age? 4 A Yes, I do see that. 5 Q On page 25 -- I'm sorry -- 1215. So the 6 page before the second paragraph under "Discussion," 7 they talk about Edelman 1992; is that right? 8 A Yes. 9 Q And the authors state, They concluded, 10 however, that despite the positive and significant 11 association, there was insufficient information to 12 infer that ovarian cancers were caused by 13 occupational exposure to asbestos -- 14 A I -- I'm sorry. I -- 15 Q Sure. 16 A -- I -- I'm lost. Where are we? 17 Q Okay. So do you see under "Discussion" -- 18 A Yes. 19 Q -- the second paragraph -- 20 A Yes. 21 Q -- I believe the second sentence? It 22 says, They concluded. 23 Are you with me? 24 A Yes. They are describing another 25 meta-analysis --</p>
Page 327	Page 329
<p>1 Q That study points out that there's an 2 inability to account for nonoccupational risk 3 factors for ovarian cancer in these studies other 4 than age; is that right? 5 MS. O'DELL: If -- if you remember. If 6 you need to see -- 7 A I -- I don't remember. 8 Q (BY MR. ZELLERS) All right. Do you have 9 the Camargo paper in front -- 10 A I -- 11 Q -- of you or would you like me to give it 12 to you? 13 A -- please. 14 Q Camargo 2011, we will mark as deposition 15 Exhibit 35. 16 (Exhibit 35 was marked for identification 17 and is attached to the transcript.) 18 A Thank you. 19 Q (BY MR. ZELLERS) Do you have that in front 20 of you now? 21 MS. O'DELL: Thank you. 22 A Yes, I do. 23 Q (BY MR. ZELLERS) Camargo. Take a look, if 24 you will, you know, on page 1216. The second 25 paragraph above "Conclusion," does Camargo and the</p>	<p>1 Q Yes. 2 A -- they concluded, yes. 3 Q This -- this is a review of different meta 4 -- 5 A Yeah. 6 Q -- analyses; is that right? 7 A Yes. 8 Q And they're describing Edelman 1992. And 9 they state, They concluded, however, that despite 10 the positive and significant association, there was 11 insufficient information to infer that ovarian 12 cancers were caused by occupational exposure to 13 asbestos because of concerns about tumor 14 misclassification, inappropriate comparison 15 populations, and the failure to take into account 16 for known risk factors. 17 Is that right? 18 A You're reading from Camargo, who is 19 quoting from a discussion by Edelman, so that -- 20 that's what it says. I -- I don't -- I don't know 21 that that's what Edelman says, but -- but yes, 22 that's the... 23 Q Wouldn't you expect to find higher rates 24 of other cancers in women using talc, like 25 mesothelioma, if they are being exposed to</p>

22 (Pages 326 to 329)



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<p>1 substantial amounts of asbestos?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A I -- I'm confused. I'm confused. Are you</p> <p>4 saying women exposed to asbestos are not getting</p> <p>5 mesothelioma?</p> <p>6 Q (BY MR. ZELLERS) Well, let me ask it this</p> <p>7 way: Are -- are women who use talc in the perineal</p> <p>8 region at greater risk of mesothelioma?</p> <p>9 A I do not know studies that have said that.</p> <p>10 Q Are women who use talc in the perineal</p> <p>11 region at greater risk of asbestosis?</p> <p>12 A In the lungs?</p> <p>13 Q Yes.</p> <p>14 A I -- I do not know those studies.</p> <p>15 Q With respect to fragrance chemicals, you</p> <p>16 have no evidence that the blood or tissue levels of</p> <p>17 any trace metals are higher in genital talc users</p> <p>18 compared to nonusers, correct?</p> <p>19 A I -- I don't know that literature at all.</p> <p>20 Q And you have no knowledge as to either the</p> <p>21 amount or concentration of different fragrance</p> <p>22 chemicals in the baby powder, correct?</p> <p>23 A I -- I do not.</p> <p>24 MR. ZELLERS: Okay. I have no further</p> <p>25 questions. My colleagues may have some questions.</p>	<p>1 Q Okay. So when -- if you answered a</p> <p>2 question, is it because you believe you understood</p> <p>3 it and that you felt able to answer it?</p> <p>4 A Yes.</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 Q (BY MS. BOCKUS) Okay. So before being</p> <p>7 hired in this case, you had not really looked at the</p> <p>8 association between talc and ovarian cancer; is that</p> <p>9 fair?</p> <p>10 A That's correct.</p> <p>11 Q The person who wrote to you first, do you</p> <p>12 remember if it was a male or a female, the attorney?</p> <p>13 A I think it was a women.</p> <p>14 Q Okay. And have you -- tell me what search</p> <p>15 you have done to locate that person's name.</p> <p>16 A I could probably search some more. I --</p> <p>17 I -- my correspondence with these lawyers that I</p> <p>18 have a document of on my computer is from July.</p> <p>19 But Mike reminded me that I must have met</p> <p>20 with them in June. So I could go through -- there</p> <p>21 are ways I can access older e-mails to look if</p> <p>22 that's important to you. I'm happy to try and find</p> <p>23 that person.</p> <p>24 Q I just was curious. There -- because you</p> <p>25 have nothing in the published literature about the</p>
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<p>1 MS. BOCKUS: Could we go off the record</p> <p>2 for just a minute to move the microphone down?</p> <p>3 THE VIDEOGRAPHER: The time is 11:16 a.m.</p> <p>4 We are off the record.</p> <p>5 (A break was taken from 1:16 a.m. to 11:17</p> <p>6 a.m.)</p> <p>7 THE VIDEOGRAPHER: The time is 11:17 a.m</p> <p>8 we are now back on the record.</p> <p>9 EXAMINATION BY COUNSEL FOR THE DEFENDANTS</p> <p>10 BY MS. BOCKUS:</p> <p>11 Q Good morning, Doctor. I introduced myself</p> <p>12 yesterday, I hope. I'm not sure I did. I'm Jane</p> <p>13 Bockus. I represent Imerys in this matter.</p> <p>14 How are you feeling today?</p> <p>15 A I'm good. Thank you.</p> <p>16 Q Have you gone back to work full time since</p> <p>17 your skiing accident?</p> <p>18 A I am primarily a researcher, so I get to</p> <p>19 choose my own hours. So I have gone back to work</p> <p>20 full time, but I often leave work a little earlier</p> <p>21 and take a rest.</p> <p>22 Q Has your injury from your skiing accident</p> <p>23 affected your ability to answer all the questions</p> <p>24 you have been asked in the last day and a half?</p> <p>25 A It has not.</p>	<p>1 etiology of ovarian cancer, correct?</p> <p>2 A I do not. And I will tell you I asked the</p> <p>3 person who contacted me what the case was about, was</p> <p>4 it an area of my expertise.</p> <p>5 And the person who contacted me, I think,</p> <p>6 was someone who knew of me from another case. And</p> <p>7 it was my researching abilities, not my content</p> <p>8 expertise, that led her to reach out to me.</p> <p>9 Q Okay. So it was with the understanding</p> <p>10 that you would start a whole new area of research in</p> <p>11 order to answer the question; is that correct?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A Yes.</p> <p>14 Q (BY MS. BOCKUS) Okay. In fact, when you</p> <p>15 appeared before congress, you stated that you're a</p> <p>16 clinical radiologist and you conduct research</p> <p>17 focusing on -- or focused on assessing the risk and</p> <p>18 benefits of medical imaging, correct?</p> <p>19 A If -- if you have my testimony there, I'm</p> <p>20 going to believe you.</p> <p>21 Q And when you have given interviews or have</p> <p>22 written opinion pieces, you identify yourself as</p> <p>23 primarily a radiologist who focuses on evaluating</p> <p>24 the risks and benefits of medical imaging, correct?</p> <p>25 MS. O'DELL: Object to the form.</p>

23 (Pages 330 to 333)

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<p style="text-align: right;">Page 334</p> <p>1 A So I have given a lot of interviews, and I 2 often identify as a professor of epidemiology and 3 biostatistics. I'm not sure what interview that you 4 are looking at. 5 I often -- often introduce myself as a 6 professor of obstetrics, gynecology, and 7 reproductive sciences. 8 And my guess is that whomever is 9 publishing the interview will choose to present me 10 in a way that they think highlights my skill. 11 But -- but my -- I'm a professor in 12 radiology and epidemiology and biostatistics, 13 obstetrics, gynecology, and a member of the Philip 14 R. Lee Institute for Health Policies Studies. 15 So I -- I get presented with whichever of 16 those first the presenter thinks might highlight my 17 expertise. 18 Q Are you board-certified in obstetrics and 19 gynecology? 20 A I'm not. 21 Q The Bradford Hill criteria, the first 22 consideration is the "strength of the association"; 23 is that correct? 24 A First criteria? Yes. 25 Q What do you consider to be a strong</p>	<p style="text-align: right;">Page 336</p> <p>1 about a quantitative association, but rather, the 2 biases and legitimacy of the association. 3 Q Are you familiar with the text "Analysis 4 of Case-Control Studies" by Breslow and Day? 5 A I -- I -- yes. 6 Q Do you find that to be a reliable text on 7 the subject of the analysis of case-control studies? 8 MS. O'DELL: Object to the form. 9 A I -- I don't know that chapter or section 10 enough to answer that question without looking at 11 it. 12 Q (BY MS. BOCKUS) But you're familiar with 13 their work? 14 A Yes. 15 Q And they're well-respected 16 epidemiologists? 17 A Yes. 18 MS. O'DELL: Object to the form. 19 Q (BY MS. BOCKUS) You make a statement in 20 your report on page 12 that the most widely accepted 21 mechanism for initiation, promotion, and progression 22 of ovarian cancer is tissue inflammation leading to 23 a series of responses that result in cancer. 24 And you have talked about that sentence a 25 bit with Mr. Zellers already.</p>
<p style="text-align: right;">Page 335</p> <p>1 association? 2 A So it overlaps a little bit with the 3 second concept of Bradford Hill in the consistency 4 of -- of the data. 5 But where the association is meaningfully 6 and legitimately documented across study designs and 7 patient populations such that the association is 8 believable and meaningful, not necessarily 9 associated with a particular point estimate of 10 association, if that's the question. 11 I don't have any particular number. It's 12 rather the entirety of the relationship, that it's a 13 meaningful quantifiable association. 14 Q Do you teach epidemiology? 15 A I do. 16 Q Can you identify textbooks that you find 17 reliable on the subject of epidemiology? 18 A The textbook that I often use to teach 19 epidemiology is a book -- I -- I'm not sure if the 20 authorship has changed over the years, but by holly 21 Cummings that talks about principles of 22 epidemiology. It's sort of the clearest version 23 that I know. 24 And -- and they -- and I haven't looked 25 this particular question up, but they wouldn't talk</p>	<p style="text-align: right;">Page 337</p> <p>1 Did you do a survey of the literature to 2 determine what was the most widely accepted 3 mechanism for initiation of ovarian cancer? 4 A I did. 5 Q And did you do a survey of the cancer 6 biology literature? 7 MS. O'DELL: Object to the form. 8 A What was the first literature you asked me 9 about? 10 Q (BY MS. BOCKUS) The literature that 11 supported your statement that the most widely 12 accepted mechanism was inflammation. 13 And you said you did a survey on the 14 inflammation literature -- or I mean on the 15 etiology -- let me start all over again. 16 Have you done a survey on articles that 17 discuss the likely mechanism for the etiology of 18 ovarian cancer? 19 A Yes, I have . 20 Q Have you -- have you -- did your survey 21 include the literature on the cancer biology -- 22 A Yes. 23 Q -- of -- 24 A Yes, it did. 25 Q -- of ovarian cancer?</p>

24 (Pages 334 to 337)

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<p>1 A Yes, it did.</p> <p>2 Q And did you find that as the issue of</p> <p>3 inflammation as an initiator of ovarian cancer is</p> <p>4 not a settled question?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A I -- I would acknowledge that -- that none</p> <p>7 of it is settled. It's just the most widely</p> <p>8 accepted, most widely supported, most wide -- widely</p> <p>9 enhanced view supported by the data, but I don't</p> <p>10 think the issue is settled.</p> <p>11 Q (BY MS. BOCKUS) In fact, there's still</p> <p>12 considerable research going on on the subject --</p> <p>13 A Yes --</p> <p>14 Q -- correct?</p> <p>15 A -- I think there is.</p> <p>16 Q In the next paragraph you talk about, for</p> <p>17 example, this is the middle -- there are</p> <p>18 well-described and accepted causal pathways</p> <p>19 linking in -- linking inflammation to bladder</p> <p>20 cancer, gastric cancer, colon cancer, et cetera.</p> <p>21 You would agree and you identify the</p> <p>22 inflammatory sometimes virus or whatever that's --</p> <p>23 that's well described and accepted for all of the</p> <p>24 different cancers that you list there, correct?</p> <p>25 For example, you identify toxic chemicals</p>	<p>1 with body powder use and ovarian cancer, correct?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A I -- I'm going to go back to say that I --</p> <p>4 I don't know what the strength of the association is</p> <p>5 with -- with these individual cancers.</p> <p>6 I -- I don't know if it's a 20 percent</p> <p>7 increase or a 500 percent increase, except for the</p> <p>8 one that I gave the example of of bladder cancer.</p> <p>9 So for bladder cancer, I gave two examples</p> <p>10 that cause inflammation of the bladder. One being</p> <p>11 toxic chemicals and the second being cigarette</p> <p>12 smoking.</p> <p>13 The toxic chemicals have a very strong</p> <p>14 relative risk of 200 or 300, where I think smoking</p> <p>15 has a relative risk of more like 1.3.</p> <p>16 And so I -- I -- I don't know it for these</p> <p>17 other cancers. But at least for bladder cancer,</p> <p>18 which I think is -- I think the second most common</p> <p>19 cancer and cigarette smoke is -- I think the</p> <p>20 association in the ballpark of 1.3.</p> <p>21 I think I have it in here. But -- so for</p> <p>22 most of these, I don't know what that number is.</p> <p>23 MS. BOCKUS: I'm going to object as</p> <p>24 nonresponsive.</p> <p>25 Q (BY MS. BOCKUS) Because the question I</p>
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<p>1 for the etiology of bladder cancer, correct?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 Q (BY MS. BOCKUS) Do you see where I'm</p> <p>4 reading?</p> <p>5 A I -- I don't see where you're reading</p> <p>6 exactly, but -- but I agree with you that I have</p> <p>7 given examples where we know the cause of the</p> <p>8 inflammation for many of those cancers.</p> <p>9 Q (BY MS. BOCKUS) You would agree that there</p> <p>10 is no equivalent literature linking ovarian cancer</p> <p>11 to talcum powder use, correct?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A I think there's a strong literature on</p> <p>14 components of the analysis. But I think for several</p> <p>15 of the examples I have given, the data are a little</p> <p>16 bit clearer and further along.</p> <p>17 So path -- HPV and cervical cancer has a</p> <p>18 longer historical data collection period when we</p> <p>19 have them --</p> <p>20 Q (BY MS. BOCKUS) And --</p> <p>21 A -- identified. So I think that's your</p> <p>22 question.</p> <p>23 Q -- so the strength of the association</p> <p>24 between HPV virus and cervical cancer is much, much</p> <p>25 stronger than any association that's been reported</p>	<p>1 asked was about the HPV virus and cervical cancer --</p> <p>2 A I don't --</p> <p>3 Q -- correct?</p> <p>4 A -- know the -- the relative --</p> <p>5 Q All right.</p> <p>6 A -- risk for that. But I -- I thought I</p> <p>7 said the only one I do know is the bladder cancer</p> <p>8 numbers.</p> <p>9 Q Has your methodology in determining what</p> <p>10 studies to include and what studies to exclude been</p> <p>11 peer reviewed in any way, shape, or form?</p> <p>12 A It has not.</p> <p>13 Q Has your math --</p> <p>14 A Oh, I'm sorry. Has my methodology been</p> <p>15 peer reviewed?</p> <p>16 Q In -- in this particular case, the method</p> <p>17 --</p> <p>18 A Okay. The method has been peer reviewed.</p> <p>19 But in this particular case, it has not.</p> <p>20 Q So no one has looked over your report and</p> <p>21 determined whether your decision -- and as I</p> <p>22 understand it, it was your decision alone, correct,</p> <p>23 as to whether to include data from a particular</p> <p>24 study or not --</p> <p>25 A Again --</p>

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<p>1 Q -- and --</p> <p>2 A -- it was a decision between myself and</p> <p>3 the -- and -- and -- and Dr. Hall --</p> <p>4 Q So --</p> <p>5 A -- just the two of us.</p> <p>6 Q -- okay. So did Dr. Hall participate in</p> <p>7 the decision-making process as to which of the</p> <p>8 case-control studies and the cohort studies to</p> <p>9 include and which to exclude?</p> <p>10 A It -- so it's -- it's a -- the answer is</p> <p>11 partly and partly not.</p> <p>12 So in terms of whether the studies were</p> <p>13 included in the final analysis, Dr. Hall was</p> <p>14 involved in that decision.</p> <p>15 But in terms of setting up the question to</p> <p>16 begin with, she was not involved in that. I -- I</p> <p>17 set that up.</p> <p>18 Q So other than you and Dr. Hall, has anyone</p> <p>19 been involved in the process of determining which</p> <p>20 studies were going to be involved -- in -- were</p> <p>21 going to be included in your systematic review and</p> <p>22 which were not?</p> <p>23 A Nobody else.</p> <p>24 Q Okay. And has anyone other than you and</p> <p>25 Dr. Hall even checked your work for transcription</p>	<p>1 Q Would you agree that you're -- at this</p> <p>2 point in time your report is not yet ready to be</p> <p>3 submitted for peer review?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A I would agree that the description in this</p> <p>6 report needs more detail, more -- to submit it to</p> <p>7 peer review. Not necessarily different work, but</p> <p>8 definitely different detail and description.</p> <p>9 Q (BY MS. BOCKUS) Have you satisfied</p> <p>10 yourself that the studies that you did include do</p> <p>11 not overlap with regard to patients; that you</p> <p>12 haven't counted the same patients multiple times?</p> <p>13 A I -- I am comfortable that I did my best</p> <p>14 to do that. But I know there were some cases where</p> <p>15 I felt like I wasn't 100 percent sure.</p> <p>16 Q And you would agree that by -- including</p> <p>17 the same cases and controls multiple times could</p> <p>18 skew the -- the data?</p> <p>19 MS. O'DELL: Object to the form.</p> <p>20 A I think that that theoretically is a</p> <p>21 concern of mine, which is why I try to you exclude</p> <p>22 them if there was overlap.</p> <p>23 On a practical level, the benefit of</p> <p>24 pooling data from multiple sources is that the final</p> <p>25 summary is less sensitive to any individual result,</p>
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<p>1 errors?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A No.</p> <p>4 Q (BY MS. BOCKUS) And has anyone other than</p> <p>5 you and Dr. Hall checked your work for mathematical</p> <p>6 errors?</p> <p>7 A No.</p> <p>8 Q You excluded all of the data from the</p> <p>9 cohort studies with the exception of the earliest</p> <p>10 reported data from the Nurses' Health Study; is that</p> <p>11 correct?</p> <p>12 A Yes.</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 Q (BY MS. BOCKUS) Did you run the -- the --</p> <p>15 the numbers to determine if there would be a</p> <p>16 difference if you included the data from all the</p> <p>17 cohort studies and if you excluded them?</p> <p>18 A So the requirement to be in our review was</p> <p>19 to have a measure of regular use of talcum powder</p> <p>20 products, and those other studies didn't have</p> <p>21 something to plug into that equation.</p> <p>22 So -- so I didn't have a number from those</p> <p>23 studies to include in a sensitivity analysis. They</p> <p>24 -- they didn't report regular use, so I -- I</p> <p>25 couldn't do what you are asking me to have done.</p>	<p>1 let alone some patients that might overlap.</p> <p>2 But I agree with you that you want to</p> <p>3 avoid that because of that concern.</p> <p>4 Q (BY MS. BOCKUS) All right. Would you turn</p> <p>5 to page 35 of your study. And I am looking at</p> <p>6 the -- right in the middle of the page, the</p> <p>7 paragraph that starts with the word, Further talc</p> <p>8 particles.</p> <p>9 But I'm going to the last sentence in the</p> <p>10 paragraph.</p> <p>11 "The greater frequency at which talc</p> <p>12 particles are discovered in ovarian cancerous tissue</p> <p>13 than in normal ovarian tissue further supports that</p> <p>14 these target -- particles may be causing cancer."</p> <p>15 You don't have a source for that. You</p> <p>16 don't cite to any study. And I would like to know</p> <p>17 where you got that information.</p> <p>18 MS. O'DELL: Objection to form.</p> <p>19 A I would have to review Heller and</p> <p>20 Henderson. No. Henderson is just cancer.</p> <p>21 So I would have to review -- review</p> <p>22 Heller, but that -- I -- I -- I don't remember what</p> <p>23 the -- cite of it. I would have to look at the</p> <p>24 articles that I cite in that paragraph and see if I</p> <p>25 could remember.</p>

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<p style="text-align: right;">Page 346</p> <p>1 Q (BY MS. BOCKUS) The next statement has to</p> <p>2 do with the reduction in incidence of ovarian cancer</p> <p>3 after tubal ligation or hysterectomy?</p> <p>4 A Yes.</p> <p>5 Q Is it not correct that that statement is</p> <p>6 true for both women who have used talcum powder</p> <p>7 product and who -- let me ask a better question.</p> <p>8 Here you're talking about that the</p> <p>9 elevated -- that studies that look at the risk of</p> <p>10 ovarian cancer associated with powder products</p> <p>11 report a reduction in risk after hysterectomy or</p> <p>12 tubal ligation, correct?</p> <p>13 A Yes.</p> <p>14 Q Isn't that also true in the general</p> <p>15 population for all women, that there -- whether they</p> <p>16 have used talcum powder products or not, that their</p> <p>17 risk of ovarian cancer is reduced by hysterectomy or</p> <p>18 oophorectomy --</p> <p>19 A Yes.</p> <p>20 Q -- or tubal ligation? I'm sorry.</p> <p>21 A Yes. It's even more reduced by</p> <p>22 oophorectomy.</p> <p>23 Q Well, sure. I misspoke.</p> <p>24 MS. BOCKUS: I believe that's all the</p> <p>25 questions I have. Thank you.</p>	<p style="text-align: right;">Page 348</p> <p>1 attorney who represents Defendant Personal Care</p> <p>2 Products Council.</p> <p>3 So for purposes of this deposition when I</p> <p>4 reference "Personal Care Products Council," I mean</p> <p>5 PCPC or CPFA or any of its predecessors. Is that</p> <p>6 okay?</p> <p>7 A Yes.</p> <p>8 Q So I want to turn to Exhibit 15, which is</p> <p>9 your reference list. And that reference list is</p> <p>10 Exhibit B of your expert report; is that correct?</p> <p>11 A Yes.</p> <p>12 Q And if you can turn to page 19 of that</p> <p>13 reference list. And just let me know when you're</p> <p>14 there.</p> <p>15 A I am there.</p> <p>16 Q And if you go about 75 percent of the way</p> <p>17 down, there's a reference to a PCPC document.</p> <p>18 Do you see that?</p> <p>19 A Yes.</p> <p>20 Q Do you happen to know what that document</p> <p>21 is?</p> <p>22 A I do not.</p> <p>23 Q Did you rely on this document --</p> <p>24 A You would have to --</p> <p>25 MS. O'DELL: Object to the form. Excuse</p>
<p style="text-align: right;">Page 347</p> <p>1 MS. O'DELL: Why don't we go off the</p> <p>2 record. I'm sorry. Do you --</p> <p>3 MR. ZELLERS: No.</p> <p>4 MR. BILLINGS-KANG: I may have two or</p> <p>5 three questions.</p> <p>6 MS. O'DELL: Oh, sorry, James. Yeah,</p> <p>7 please.</p> <p>8 THE VIDEOGRAPHER: We are still on?</p> <p>9 MS. O'DELL: Yes.</p> <p>10 THE VIDEOGRAPHER: Do we want to go off?</p> <p>11 MR. BILLINGS-KANG: Yeah.</p> <p>12 MS. BOCKUS: We need to go off to move the</p> <p>13 mic.</p> <p>14 THE VIDEOGRAPHER: The time is 11:37 a.m.</p> <p>15 We are going off the record.</p> <p>16 (A break was taken from 11:37 a.m. to</p> <p>17 11:40 a.m.)</p> <p>18 THE VIDEOGRAPHER: The time is 11:40 a.m.</p> <p>19 We are now back on the record.</p> <p>20 EXAMINATION BY COUNSEL FOR THE DEFENDANTS</p> <p>21 BY MR. BILLINGS-KANG:</p> <p>22 Q Good morning, Dr. Smith-Bindman. How are</p> <p>23 you?</p> <p>24 A Good.</p> <p>25 Q My name is James Billings-Kang. I'm an</p>	<p style="text-align: right;">Page 349</p> <p>1 me. Object to the form. If -- if --</p> <p>2 A -- you would have to tell me what it is to</p> <p>3 know if --</p> <p>4 MS. O'DELL: -- or show it to her if</p> <p>5 you --</p> <p>6 MR. BILLINGS-KANG: Sure.</p> <p>7 MS. O'DELL: -- have a question about it.</p> <p>8 Q (BY MR. BILLINGS-KANG) But for purposes of</p> <p>9 formulating your opinion in the expert report, did</p> <p>10 you rely on any PCPC-produced documents?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A You would have to show --</p> <p>13 MS. O'DELL: Put --</p> <p>14 A -- it to me.</p> <p>15 MS. O'DELL: -- just put it in front of</p> <p>16 her if you're going to ask her a question about it</p> <p>17 so she can --</p> <p>18 Q (BY MR. BILLINGS-KANG) I'm just asking:</p> <p>19 Based on your memory, do you recall using any</p> <p>20 PCPC-produced document to formulate your opinion.</p> <p>21 MS. O'DELL: I would -- I would just</p> <p>22 object to the form.</p> <p>23 Q (BY MR. BILLINGS-KANG) That's --</p> <p>24 MS. O'DELL: None of --</p> <p>25 Q (BY MR. BILLINGS-KANG) -- that's fine.</p>

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<p>1 You can answer --</p> <p>2 MS. O'DELL: None of that --</p> <p>3 Q (BY MR. BILLINGS-KANG) -- yes or no, if</p> <p>4 you remember.</p> <p>5 MS. O'DELL: -- none of us would be</p> <p>6 expected to remember a document based on a Bates</p> <p>7 number.</p> <p>8 Q (BY MR. BILLINGS-KANG) Well, I'm asking</p> <p>9 her just generally PCPC-produced documents, if she</p> <p>10 relied on any of those --</p> <p>11 MS. O'DELL: Objection.</p> <p>12 Q (BY MR. BILLINGS-KANG) -- to formulate her</p> <p>13 opinion?</p> <p>14 MS. O'DELL: Object to the form. I'm</p> <p>15 putting that --</p> <p>16 MR. BILLINGS-KANG: Sure.</p> <p>17 MS. O'DELL: -- that Bates number in front</p> <p>18 of her. And if you --</p> <p>19 MR. BILLINGS-KANG: Sure.</p> <p>20 MS. O'DELL: -- remember, you remember.</p> <p>21 A This is a document that lists different</p> <p>22 research studies that have been done over time. Is</p> <p>23 that the document that we're --</p> <p>24 Q (BY MR. BILLINGS-KANG) Well, I -- I'm not</p> <p>25 too sure. This is a document you listed in the</p>	<p>1 itself.</p> <p>2 Q Just --</p> <p>3 A I don't remember --</p> <p>4 Q -- the document --</p> <p>5 A -- seeing --</p> <p>6 Q -- itself.</p> <p>7 A -- this -- I don't remember seeing this</p> <p>8 document.</p> <p>9 Q Okay. You can -- you can put that away.</p> <p>10 And I will go to your expert report that's</p> <p>11 Exhibit 2, page 14. Just let me know when --</p> <p>12 A I'm there.</p> <p>13 Q -- you're there. And this -- the first</p> <p>14 paragraph under "Asbestos," it's about halfway in</p> <p>15 that first paragraph beginning with, Because of</p> <p>16 concern that asbestos was present in talcum powder</p> <p>17 products in the known carcinogenicity of asbestos,</p> <p>18 it has been reported that voluntarily guidelines</p> <p>19 were established by the cosmetic industry in 1976 to</p> <p>20 limit the content of asbestos fibers in commercial</p> <p>21 talc preparations.</p> <p>22 Did I read that correctly?</p> <p>23 A You did.</p> <p>24 Q And these are your words, correct?</p> <p>25 A Yes, they are.</p>
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<p>1 reference list.</p> <p>2 A I -- I'm just trying to make sure that I'm</p> <p>3 looking at the document that you are --</p> <p>4 Q According to your counsel, this is what's</p> <p>5 been identified on page 19 of the reference list.</p> <p>6 A I -- I do not remember this document.</p> <p>7 This --</p> <p>8 Q Okay.</p> <p>9 A -- document is just a list of studies.</p> <p>10 Q So you do not recall whether you relied on</p> <p>11 this document in formulating your opinion?</p> <p>12 A My --</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A -- opinion is not based on the -- on a --</p> <p>15 a list of studies.</p> <p>16 Q (BY MR. BILLINGS-KANG) Okay. So that's --</p> <p>17 that's a -- that's a yes, you do not -- you did not</p> <p>18 rely on this document in formulating your opinion?</p> <p>19 A I -- I don't remember seeing this</p> <p>20 document. As I'm going through this document, there</p> <p>21 are a lot of studies that I reviewed that I did rely</p> <p>22 on.</p> <p>23 So I don't know if you're asking me if I</p> <p>24 relied specifically on some of the items in here</p> <p>25 that I have relied on or the -- this document</p>	<p>1 Q And what did you mean by "voluntarily</p> <p>2 guidelines"?</p> <p>3 A I -- I have read a lot about the</p> <p>4 guidelines. And it -- the idea was that the</p> <p>5 industry decided to self-regulate and to do what</p> <p>6 they could to remove the asbestos, is my</p> <p>7 understanding of what that was as opposed to being</p> <p>8 required to submit testing to document that they had</p> <p>9 done so.</p> <p>10 Q And -- and what did you rely upon for this</p> <p>11 particular sentence?</p> <p>12 A This particular sentence is repeated in --</p> <p>13 in at least half of the papers that I have read that</p> <p>14 are epidemiology papers.</p> <p>15 It's repeated in all of the news studies.</p> <p>16 It's repeated in reports by consumer organizations,</p> <p>17 by the FDA, by the recent Canadian report, which I</p> <p>18 didn't have in hand.</p> <p>19 But it's something that I -- I have read a</p> <p>20 lot -- a great deal, that there were voluntarily</p> <p>21 standards that were established by the industry.</p> <p>22 Q And so did you read any publication or</p> <p>23 whatever reliance materials that you had that</p> <p>24 described these guidelines as anything else other</p> <p>25 than voluntarily guidelines?</p>

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<p style="text-align: right;">Page 354</p> <p>1 A I -- I -- I did not. I looked for 2 documents like that. I was not able to find them. 3 Required -- requirements, I was not able to find. 4 MR. BILLINGS-KANG: Okay. That's all I 5 have. 6 MS. O'DELL: Why don't we take a short 7 break. 8 THE VIDEOGRAPHER: The time is 11:45 a.m. 9 We are now off the record. 10 (A break was taken from 11:45 a.m. to 11 12:15 p.m.) 12 THE VIDEOGRAPHER: The time is 12:15 p.m. 13 We are now back on the record. 14 EXAMINATION BY COUNSEL FOR THE PLAINTIFFS 15 BY MS. O'DELL: 16 Q Dr. Smith-Bindman, I have just a few 17 questions for you. First, during all of your work 18 in this case, was it your understanding that you 19 were serving as an expert consultant? 20 A Yes. 21 Q And you know, throughout the early 22 meetings in June, I believe, of 2017, where you met 23 with Plaintiffs' counsel, did Plaintiffs' counsel 24 provide information regarding their theories of the 25 talcum powder litigation?</p>	<p style="text-align: right;">Page 356</p> <p>1 MR. ZELLERS: Objection, form. 2 Q (BY MS. O'DELL) Let me strike that and 3 start again. Did your meta-analysis replicate what 4 had been published in the literature? 5 A The -- 6 MR. ZELLERS: Form. 7 A -- the results of my meta-analysis and the 8 previous ones are nearly identical. So yes, it was 9 a very close replication. 10 Q (BY MS. O'DELL) And you have mentioned 11 your intent to publish your -- your meta-analysis, 12 your systematic review. And I believe you testified 13 that in the published version, you would add 14 additional detail. 15 What did you mean by that? 16 A So the analysis that I have done is 17 complete. But the presentation of the results in a 18 paper would require more beautiful graphics, would 19 require explaining our inclusion and exclusion 20 criteria more fully than I did in this published 21 report. Things like that. 22 And that actually is a substantial part of 23 the writing of a scientific paper, sort of 24 explaining every step of what you did, and so I 25 would have to do more of that to publish this study.</p>
<p style="text-align: right;">Page 355</p> <p>1 A Yes. 2 Q And have you been paid by Plaintiffs' 3 counsel for all the work that you have billed in 4 this case? 5 A Yes, I have. 6 Q Okay. You have been asked a number of 7 questions about the meta-analysis, the systematic 8 review that you performed on the regular use of -- 9 of talcum powder. 10 Would you have reached your opinions in 11 this case without having performed that analysis? 12 A My systematic review ended up with the 13 same estimates as essentially all of the other 14 well-done systematic reviews. 15 And it was very helpful for me to confirm 16 the results. But yes, it's the same as the other 17 studies, and so my -- my conclusion about the 18 causality of talcum powder products and ovarian 19 cancer would be exactly the same, even without mine. 20 It just made me a little more comfortable 21 that I was certain about the -- the results 22 presented by other people. 23 Q And in a sense, the analysis that you did 24 replicated the work that had been published in the 25 -- in the literature?</p>	<p style="text-align: right;">Page 357</p> <p>1 Q Is there sufficient detail in the -- in 2 your report regarding your methodology, as well as 3 in the documentation provided in the spreadsheets 4 to -- for someone to replicate the work that you 5 have done? 6 MR. ZELLERS: Objection, form. 7 A I believe that if someone used the 8 software that we said and had the inclusion criteria 9 that we led out -- set out, that they would get the 10 -- the same results as we got. 11 And I think the fact that our review 12 provides the same results as other systematic 13 reviews sort of, you know, also supports that. But 14 yes, I think someone could easily replicate our -- 15 our analysis. 16 Q (BY MS. O'DELL) Okay. You were asked a 17 number of -- before I do that, let me ask you: Can 18 there be multiple causes of ovarian cancer? 19 A Absolutely. I -- I describe in the 20 report, a whole number of different risk factors for 21 ovarian cancer. 22 Q And in a -- in a patient -- hypothetically 23 in a patient who has a BRCA1 mutation, possibly has 24 other risk factors for ovarian cancer, and also uses 25 talcum powder products, under those circumstances,</p>

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<p style="text-align: right;">Page 358</p> <p>1 would talcum powder products be a contributing cause 2 of her cancer? 3 MR. ZELLERS: Objection, form. 4 A I think patients can have multiple risk 5 factors and causes of -- of cancer. Some causes, 6 you would imagine, would be quite synergistic. 7 So having both together would be worse 8 than twice having either of those alone. So it 9 would be worse than having -- it -- it would be more 10 than double the initial, because they would be 11 basically enhancing. 12 So if -- if some risk factors caused lots 13 of oxidative stress and another enhanced that 14 oxidative stress and prevented repair or cell 15 apoptosis, you would get even more impact. 16 So yes, I would say multiple risk factors 17 for most diseases occur concurrently, and sometimes 18 they enhance or are synergistic. 19 Q (BY MS. O'DELL) Can asbestos be inhaled 20 and cause ovarian cancer? 21 MR. ZELLERS: Objection, form; foundation. 22 A Absolutely. The -- the IARC 2012 report 23 was primarily on the basis of inhalation of 24 asbestos. 25 Q (BY MS. O'DELL) Can fibrous talc be</p>	<p style="text-align: right;">Page 360</p> <p>1 not disclosed in Dr. Smith-Bindman's expert report. 2 A Can I read? Just on page 14, The results 3 were consistent, significant, and documented a 4 strong and compelling causal association between 5 exposure to asbestos and ovarian cancer largely 6 result in the association from cohort studies of 7 women with substantial occupational exposures. 8 That -- that was the -- 9 Q (BY MS. O'DELL) Okay. Let me -- let me 10 ask you to -- to turn, Dr. Smith-Bindman, to the 11 Langseth paper that was marked as Exhibit 30 by 12 counsel for J&amp;J. 13 And specifically to turn to page 2 of the 14 paper to Figure 1. 15 A Yes. 16 Q You were asked a number of questions about 17 whether the studies that had confidence intervals 18 that cross one were essentially by chance. In other 19 words, they -- they did not speak to a potential 20 increased risk in ovarian cancer as a result of 21 talcum powder use. 22 Are the -- what's your analysis of those 23 studies and whether, as counsel put it, it was 24 equivalent to a coin toss? 25 A So if there was no relationship between</p>
<p style="text-align: right;">Page 359</p> <p>1 inhaled and cause ovarian cancer? 2 A I -- 3 MR. ZELLERS: Objection, form; foundation. 4 A -- yes. 5 Q (BY MS. O'DELL) And what's your basis for 6 that statement? 7 MR. ZELLERS: Same objections. None of 8 this was in her report. None of this has been in 9 her opinions. 10 These are all new opinions. So inhalation 11 has not been any part of her testimony or her 12 opinion. 13 MS. O'DELL: Inhalation is mentioned in 14 her report. 15 A I -- I -- you know, the -- the chapter on 16 asbestos and occupational exposure and IARC report 17 is -- is about inhalation. 18 I'm not sure if I -- I was explicit about 19 the route, but that is where the data come from for 20 asbestos, as well as fibrous talc. 21 And those articles talk about the fact 22 that there might be other exposures in addition, but 23 they're primarily inhalation studies. 24 MR. ZELLERS: Again, object to what the 25 defense views as a completely new opinion that was</p>	<p style="text-align: right;">Page 361</p> <p>1 ovarian cancer and exposure to talcum powder 2 products, you would expect the forest plot in 3 Figure 1 to have half of the point estimates be 4 above one, saying there's a risk; and half of the 5 point estimates being below one, saying there isn't 6 a risk. 7 In fact, every one of the studies on this 8 table is at or above one. It's to the right. So to 9 get that by chance is highly, highly, highly 10 unlikely. 11 The best estimate is -- the point estimate 12 in all of those are very different than one. 13 And so to call that by chance doesn't make 14 sense. The fact that for an individual study, the 15 confidence interval overlap one doesn't mean it's by 16 chance. 17 So again, by chance would mean half the 18 studies have a positive association, half have a 19 protective. 20 And in fact, every one of the studies has 21 a value that's either substantially greater than one 22 or just a little greater than one. 23 Q Okay. You were asked questions about 24 starting -- in reference to the Langseth paper you 25 were asked questions about the -- the pooled odds</p>

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<p style="text-align: right;">Page 362</p> <p>1 ratio for hospital-based studies and the focus on 2 that finding being that it was not a statistically 3 significant increased risk. 4 Did the Berge paper also look at a pooled 5 analysis of the hospital-based studies? 6 A She did. If you look at Table 2, Table 2 7 shows the results of the case-control studies that 8 were hospital based versus community based. 9 And those individual group of 10 hospital-based studies are statistically 11 significant. 12 But I would point out that in this case 13 the -- they report the relative risk of a hospital 14 based versus community based. They're relatively 15 similar. They're both significant, and they're 16 relatively similar, which is what I concluded from 17 Langseth. They're very similar. 18 Q Okay. You were asked about studies 19 relating to migration. And the specific -- the 20 specific question, as I wrote it down was: Is there 21 a study that demonstrates talc on the -- applied to 22 the perineum, traveling to the -- or migrating to 23 the ovary, and you said, No. 24 What evidence are you relying on to 25 support your opinion that talcum powder can migrate</p>	<p style="text-align: right;">Page 364</p> <p>1 There have been studies of sperm, both 2 living and dead, going in both directions. So it's 3 not just the mobile sperm, but the dead sperm. 4 Carbon particles -- you know, a tiny 5 study -- but have been shown to move -- radioactive 6 material has been seen to move. Material on gloves 7 has been seen. 8 So it's a wide-open system. The idea that 9 we think of that as being a barrier system is just 10 false. 11 Now, I don't know of an individual study 12 that has put talc on the perineum. I think that's, 13 unfortunately, not an ethical study to do. And I 14 don't know of such a study or why you would do such 15 a study. 16 But to think that there's any barrier 17 between the perineum and the vagina makes no sense 18 whatsoever. 19 Q Let me transition to talk about 20 inflammation for a moment, and specifically 21 inflammation as a cause of ovarian cancer first. 22 What evidence are you relying on to 23 support your opinion that inflammation -- chronic 24 inflammation causes ovarian cancer? 25 A Okay. So there's an enormous amount of</p>
<p style="text-align: right;">Page 363</p> <p>1 when applied -- applied to the genital area to the 2 ovary? 3 A So I was asked a very narrow question, is 4 there a study that talks about transport from the 5 perineum. 6 But in fact, there is extensive evidence 7 that particles from the perineum could get to the 8 ovary and do get to the ovary. 9 And part of that is the perineum is 10 basically equivalent to the vagina. It is one open 11 system to the ovary. 12 And so my evidence for that is 13 several-fold. First, I'm a clinical radiologist, 14 and I do a lot of procedures in women where I am 15 putting catheters in the vagina and injecting fluid 16 that goes to the uterus, to the tubes. I watch the 17 fluid spill. It's a wide-open system. 18 Occasionally patients have complications 19 that don't let me do that, and I might inject fluid 20 literally on the perineum to get a backlash to the 21 ovaries. And it's a wide-open connected system. 22 All of our textbooks talk about it being a 23 bi-directional system. You know, infection goes 24 both directions. Retrograde menstruation and 25 menstruation go both directions.</p>	<p style="text-align: right;">Page 365</p> <p>1 literature that understands what we see when there's 2 inflammation, what kind of changes you see on a 3 cellular level. 4 So you see increase in pro oxidation, a 5 reduction in antioxidation. You see increase in 6 cell turnover, reduction in cell death, expression 7 of inflammatory agents, cellular changes at the DNA 8 level that leads to greater expression. 9 We -- we understand those pathways. And 10 those pathways occur both with talc exposure and in 11 the setting of things that cause ovarian cancer. 12 So I -- in my reference list, I reference 13 a whole bunch of references -- Saed references, 14 Shawn (phonetic) references, Ness references. 15 There's really enormous numbers of references. 16 I -- in my documents I have Shukla 17 references, Buz'Zard references, Hamilton references 18 that talk away sort of these inflammatory pathways 19 and biologic mechanisms that lead to changes that go 20 along with inflammation. 21 Q I know you have reviewed Dr. Saed's 22 research in regard to whether talcum powder causes 23 inflammation in vitro. 24 First, let me ask you this: Does 25 Dr. Saed's work support the conclusion that</p>

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<p style="text-align: right;">Page 366</p> <p>1 Johnson's baby powder causes inflammation? 2 MR. ZELLERS: Objection, form. 3 A So Saed specifically looked at Johnson 4 baby powder, so his results specifically pertained 5 to Johnson baby powder. 6 He looked at several different measures 7 that -- I have just mentioned inflammation. So he 8 looked specifically at oxidative stress, the up 9 regulation or down regulation of -- 10 THE COURT REPORTER: The? 11 A -- up regulation or pro oxidants, down 12 regulation of antioxidants. He looked at cell 13 proliferation. He looked at SNPS point mutations 14 that are associated with this. 15 THE COURT REPORTER: Snips? 16 A S N P S, SNPS. 17 THE COURT REPORTER: Because you're facing 18 that way, and the mic is here. Thanks. 19 A And showed substantial changes to talcum 20 powder to all of these. I -- I was really quite 21 impressed with the consistency in these markers of 22 inflammation. 23 Some of them overlap clinical markers we 24 use. Like CA125 went up very strongly just like it 25 goes up for ovarian cancer.</p>	<p style="text-align: right;">Page 368</p> <p>1 do that. That's beyond me. But that's what this 2 whole model is, to try to help you understand what 3 the effect mechanistically is from these changes. 4 Q (BY MS. O'DELL) And is the use of that 5 model in scientific research generally accepted? 6 A Highly. 7 MR. ZELLERS: Objection, form. 8 A My understanding is that is the basis for 9 much of the research that comes -- that happens at 10 my research institution. 11 Q (BY MS. O'DELL) Just to make sure that the 12 record is clear, Dr. Smith-Bindman, in -- I asked 13 the question: Is the use of that model in 14 scientific research generally accepted? I'm not 15 sure your answer came through. What's your answer? 16 MR. ZELLERS: For your -- just objection, 17 form. Go ahead. 18 A Yes. I -- I said that that's a very 19 common model at UCSF. 20 Q Okay. 21 MS. O'DELL: I have nothing further. 22 Thank you. 23 MR. ZELLERS: Let's take a break for a 24 couple of minutes. 25 THE VIDEOGRAPHER: The time is 12:34 p.m.</p>
<p style="text-align: right;">Page 367</p> <p>1 So he very clearly showed this. And the 2 results he showed were not different than those that 3 Shukla showed, that Buz/Zard showed, that -- the 4 expression in genes. 5 He -- he just had it in a very compelling 6 experiment where he showed dose response, where he 7 showed the control didn't have the changes, but that 8 the talc powder products did have the changes. 9 And so he identified, in this cellular 10 cell line model, all of the changes that you would 11 expect from inflammation. So I think the results 12 were very compelling. 13 I -- I was asked if kind of that 14 experiment has any relevance in humans. And I would 15 say it would be nice to do that experiment in 16 humans. 17 But you can't do that experiment in 18 humans. And that's what -- 19 THE COURT REPORTER: Wait. 20 A -- you can't do such an experiment in 21 humans. So -- so that is what sort of cellular 22 studies are -- are meant to approximate. 23 There's no direct translation, so how much 24 you put in the cell versus how much you put in the 25 patient, I -- you know, I don't know how you would</p>	<p style="text-align: right;">Page 369</p> <p>1 We are now off the record. 2 (A break was taken from 12:34 p.m. to 3 12:41 p.m.) 4 THE VIDEOGRAPHER: The time is 12:41 p.m. 5 We are now back on the record. 6 EXAMINATION BY COUNSEL FOR THE DEFENDANTS 7 BY MS. BOCKUS: 8 Q Doctor, you made a comment about the fact 9 that there can be a synergistic effect between 10 different risk factors; is that correct? 11 A Yes. 12 Q That is something that can be studied, 13 correct? 14 A Yes. 15 Q There are studies that can be designed to 16 determine whether there's a synergistic effect 17 between, say, BRCA mutation carriers and women who 18 have regularly used talcum powder -- 19 A Yes. 20 Q -- correct? 21 That study has not been done, correct? 22 A Not that I know of. 23 Q In fact, are you familiar or aware of any 24 studies that have looked for a synergistic effect 25 between regular talc use and any other risk factors</p>

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<p style="text-align: right;">Page 370</p> <p>1 for ovarian cancer?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A I would have to look through my papers</p> <p>4 with that question in mind. I know some of the</p> <p>5 papers have looked at BRCA, but I can't remember if</p> <p>6 they sort of stratified the results by -- with or</p> <p>7 without BRCA, so I -- I'm not sure of the answer to</p> <p>8 that.</p> <p>9 I was more speaking about, from work that</p> <p>10 I do, the idea of synergy between risk factors. And</p> <p>11 one of those is BRCA and radiation exposure. So</p> <p>12 I -- I -- I meant generally it can be the case. I</p> <p>13 didn't mean to suggest we know what it is for this.</p> <p>14 Q (BY MS. BOCKUS) Okay. Then you spoke</p> <p>15 about the female reproductive system being a</p> <p>16 wide-open system.</p> <p>17 What procedure are you doing when you are</p> <p>18 putting fluid on a women's perineum to see if it</p> <p>19 goes to the ovaries?</p> <p>20 A I apologize. So the primary procedures</p> <p>21 would be a hysterosonogram, which we're putting</p> <p>22 water into the uterus and the tubes mostly to look</p> <p>23 for patency.</p> <p>24 But it turns out we end up needing to do</p> <p>25 procedures in postop patients, not infrequently,</p>	<p style="text-align: right;">Page 372</p> <p>1 Q Do you know if anything about what you</p> <p>2 just described has any correlation to the way in</p> <p>3 which women use talcum powder in their perineal</p> <p>4 region?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A I -- I don't know what -- how women use</p> <p>7 talcum powder on their perineum.</p> <p>8 Q (BY MS. BOCKUS) Do you know what</p> <p>9 percentage of sperm that are placed in a women's</p> <p>10 vagina make it to the ovaries?</p> <p>11 A Only from child cartoons that make it seem</p> <p>12 like it's a competitive race. But percentagewise, I</p> <p>13 don't know.</p> <p>14 Q Do you have any reason to believe that</p> <p>15 talc makes it from the vagina to the ovaries in</p> <p>16 greater percentage than sperm?</p> <p>17 A I -- I -- I would guess that that's not</p> <p>18 the case.</p> <p>19 MS. BOCKUS: That's all I have.</p> <p>20 MR. ZELLERS: I have just a couple.</p> <p>21 EXAMINATION BY COUNSEL FOR THE DEFENDANTS</p> <p>22 BY MR. ZELLERS:</p> <p>23 Q Dr. Smith-Bindman, did you discuss with</p> <p>24 Plaintiffs' counsel, calling Dr. Hall on our break</p> <p>25 between yesterday's first session and today's</p>
<p style="text-align: right;">Page 371</p> <p>1 where we might be looking for connections between</p> <p>2 different structures, preop or postop.</p> <p>3 In the ballpark of 10 percent of women to</p> <p>4 20 percent have cervical stenosis, and you can't</p> <p>5 catheterize.</p> <p>6 Or there might be some reason we don't</p> <p>7 want to catheterize or put the tubes in the vagina.</p> <p>8 We might put the tube directly on the perineum and</p> <p>9 see if we can create kind of a -- a way to keep,</p> <p>10 let's say, a balloon in place and then inject in a</p> <p>11 retrograde fashion.</p> <p>12 So it feels like it comes out probably</p> <p>13 every couple of months. But we're actually pretty</p> <p>14 far from the cervix. And we're injecting usually</p> <p>15 water or sometimes contrast and then looking mostly</p> <p>16 with ultrasound, but sometimes with fluoroscopy.</p> <p>17 Q And when you say "inject," that means with</p> <p>18 some degree of pressure, you're putting the water or</p> <p>19 other fluid into the vagina?</p> <p>20 A There is some degree of pressure, yes.</p> <p>21 Q And when you do that, is the patient's</p> <p>22 head lower than her hips?</p> <p>23 A Not -- not usually, no.</p> <p>24 Q Is she on her back?</p> <p>25 A Yes.</p>	<p style="text-align: right;">Page 373</p> <p>1 session?</p> <p>2 MS. O'DELL: I'm going to ask -- ask</p> <p>3 you -- instruct you not to answer questions</p> <p>4 regarding discussions with counsel.</p> <p>5 MR. ZELLERS: The defense agreed to split</p> <p>6 this deposition of Dr. Smith-Bindman over two days</p> <p>7 on the expressed condition that the extended break</p> <p>8 not be used for preparation.</p> <p>9 The witness and Plaintiffs' counsel</p> <p>10 violated that understanding. Further, it's entirely</p> <p>11 inappropriate for an expert witness to consult with</p> <p>12 a consulting expert during a break.</p> <p>13 We move to strike all of</p> <p>14 Dr. Smith-Bindman's testimony and will take the</p> <p>15 issue to court.</p> <p>16 MS. O'DELL: The record is clear that</p> <p>17 counsel did not speak with Dr. Smith-Bindman last</p> <p>18 night. There was no preparation done between the</p> <p>19 conclusion of the deposition yesterday and the</p> <p>20 beginning of the deposition this morning. I think</p> <p>21 the record has been clear on that.</p> <p>22 That was -- we agreed to do that. We had</p> <p>23 not -- we were not compelled to do that. Because as</p> <p>24 counsel is aware, the deposition protocol allows</p> <p>25 both parties, when they're putting up their</p>

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247:16 310:3 348:12 351:5 <b>19103</b> 377:4 <b>1976</b> 269:12 352:19 <b>1992</b> 328:7 329:8	<b>2018</b> 259:15 260:2 282:5 282:7 283:4 298:9 <b>2019</b> 245:16 246:10 253:2,8 298:10,21 376:24 377:23 <b>202-828-5356</b> 250:9 <b>21</b> 273:7 <b>210-554-5549</b> 249:10 <b>212-735-2453</b> 248:21 <b>213-430-3301</b> 248:11 <b>218</b> 247:8 <b>221,000</b> 269:2 <b>25</b> 260:23 307:21 328:5 <b>250</b> 246:8 253:11 <b>254</b> 251:6 <b>259</b> 251:12 <b>26</b> 308:25 309:10,19 311:11 <b>261</b> 251:14 <b>27</b> 311:11 <b>2738</b> 245:9 <b>276</b> 251:17 <b>28</b> 251:12 259:6,11 260:3 <b>29</b> 251:14 261:2,5 <b>297</b>	251:20 <hr/> <b>3</b> <hr/> <b>3</b> 256:15 266:13 <b>3,000</b> 261:1 <b>30</b> 251:17 269:12 276:14,15 360:11 <b>300</b> 340:14 <b>31</b> 251:20 297:9,10 <b>317</b> 251:22 <b>319</b> 251:24 <b>32</b> 251:22 317:8,9 <b>324</b> 252:2 <b>327</b> 252:4 <b>33</b> 251:24 257:25 319:9,10 <b>331</b> 251:9 <b>334-269-2343</b> 247:11 <b>34</b> 252:2 257:25 324:18,23 325:1,3 <b>347</b> 251:8 <b>35</b> 252:4 327:15,16 345:5 <b>354</b> 251:7 <b>36103</b> 247:9 <b>369</b> 251:9 <b>372</b> 251:6	<b>39</b> 312:25 <hr/> <b>4</b> 248:18 <b>4.5</b> 311:7 <b>4.7</b> 310:18 311:7 <b>4.9</b> 310:18 <b>41</b> 290:7 <b>42</b> 283:13 <b>42nd</b> 248:8 <b>47</b> 268:19 <b>4th</b> 250:18 <hr/> <b>5</b> 297:14,19 <b>50,000</b> 322:19 <b>500</b> 340:7 <b>512-391-0197</b> 249:20 <b>515</b> 248:7 <b>51st</b> 377:3 <hr/> <b>6</b> 6/1/17 251:12 <b>600</b> 250:19 <b>61,000</b> 270:11 <b>63102</b> 250:20	<hr/> <b>7</b> <hr/> <b>75</b> 348:16 <b>78205</b> 249:8 <b>78701</b> 249:18 <hr/> <b>8</b> <hr/> <b>8</b> 245:16 246:10 253:2,8 <b>816</b> 249:16 <b>877-370-3377</b> 377:5 <hr/> <b>9</b> <hr/> <b>9:26</b> 246:9 253:3,9 <b>90</b> 247:23 <b>900</b> 247:24 <b>90071</b> 248:9 <b>924</b> 269:2 <b>92660</b> 247:17 <b>94111</b> 246:9 <b>975</b> 250:6
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# Exhibit 65

## C H A P T E R N I N E

*Gamete Transport  
and Fertilization***Introduction**

The process of *fertilization*, or *conception*, involves fusion of the nucleus of a male gamete (sperm) and a female gamete (ovum) to form a new individual. Because each gamete is haploid (N), fertilization restores the normal diploid (2N) chromosomal complement. Fertilization, however, is more than the simple fusion of gametes in that it is preceded by and requires a series of precisely timed events. Once sperm are deposited in the female reproductive tract, they travel a relatively long distance and overcome several obstacles before reaching the ovum. Similarly, the ovum travels through a portion of the female reproductive tract before it is fertilized. Not only do the gametes move to the appropriate regions of the female tract, but they undergo important physical and biochemical maturations that are a prerequisite for fertilization. Abnormalities in these maturational or transport processes, as well as in fertilization itself, can lead to infertility, spontaneous abortion (miscarriage), or birth defects.

**Semen Release**

After leaving the epididymides, sperm enter the vasa deferentia, which are long paired ducts serving as sperm storage and transport organs (see Chapter 4). Secretions of the male sex accessory glands (*seminal plasma*) mix with the sperm during ejaculation to form *semen* or *seminal fluid*. It has been theorized that the entire reserve of sperm in the epididymides and vasa deferentia would be depleted if an adult male had 2.4 ejaculations per day for 10 consecutive days. However, this normally does not occur, even with such Herculean ejaculation frequency because new sperm are produced continuously by the testes—about 200 million per day! Thus, frequent ejaculation is not an effective method of contraception.

Semen is released in three stages. Before male orgasm, a small amount of semen comes from the bulbourethral glands. In the second stage, the majority of semen is released; most of the seminal plasma of this stage comes from the seminal vesicles and prostate gland. In the third stage, another small amount of fluid produced by the seminal vesicles is exuded. Most of the sperm are expelled in the second stage, but some sperm are present in the semen of the first and third stages. Because sperm are present in the first stage, pregnancy can occur without male orgasm, which is one reason why *coitus interruptus* (withdrawal of the penis before ejaculation) is not an efficient method of birth control (see Chapter 14).

Contents of Seminal Plasma

Seminal plasma contains several substances, but the precise function of many of these components is not known. We do know, however, that some of them have roles in the maintenance, maturation, and transport of sperm. Water is present, which serves as a liquid vehicle for the sperm and seminal plasma constituents. Mucus from the bulbourethral glands serves as a lubricant for the passage of semen through the male reproductive tract. The prostate gland and the bulbourethral glands both secrete buffers, which neutralize the acidity in the male urethra and in the vagina. Some nutrients for sperm are present in the seminal plasma deposited in the vagina, the major ones being the sugar fructose and citric acid (from the seminal vesicles). *Carnitine*, concentrated from the blood by the epididymis, is also found in the seminal plasma. This chemical is involved in the metabolism of fatty acids, with the metabolites being used as another nutrient source for the sperm. Another constituent of seminal plasma secreted by the epididymis is *glycerylphosphocholine*. The enzyme *diesterase* in the uterus hydrolyzes (breaks down) this molecule, and the products of this digestion are used by the sperm as nutrients. Other enzymes secreted by the prostate gland and seminal vesicles are involved in the clotting and subsequent liquefaction of semen in the vagina. Human seminal plasma contains extremely high amounts of zinc (which may have antibacterial activity), and men with low zinc content tend to have a higher incidence of infertility. Finally, some kinds of prostaglandins are secreted into the seminal plasma, mostly by the seminal vesicles. Prostaglandins in seminal plasma may be involved in sperm transport. Finally, seminal plasma contains ATP, and men with low semen ATP levels tend to have lower fertility. Table 9-1 summarizes the sources of the major components of seminal plasma.

Table 9-1 Some Characteristics of Human Semen

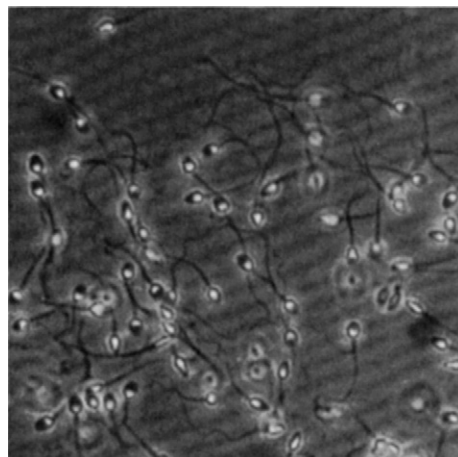
General properties			
Creamy texture: gray to yellow color			
Average volume: 2.5–3.5 ml after 3 days of abstinence (range, 2–6 ml)			
Fertility index (minimum qualifications for male fertility):			
1. At least 20 million sperm/ml			
2. At least 40% sperm must show vigorous swimming			
3. At least 60% sperm must have normal shape and size			
pH: 7.35–7.50 (slightly basic)			
Sources and major components of seminal plasma			
<b>Epididymis (a slight amount)</b>	<b>Seminal vesicles (about two-thirds of total volume)</b>	<b>Prostate gland (about one-third of total volume)</b>	<b>Bulbourethral glands (a few drops)</b>
Water	Water	Water	Water
Carnitine (a nutrient)	Fructose (a nutrient)	Bicarbonate buffers (neutralize vaginal pH)	Buffers (neutralize vaginal pH)
Glycerylphosphocholine (a nutrient)	Fibrinogen (clots semen)	Fibrinogenase (clots semen)	
	Ascorbic acid (a nutrient)	Fibrinolytic enzyme (liquifies semen)	Mucus (lubrication)
	Most of the prostaglandins (contract the vas deferens)	Citric acid (a nutrient)	
		A little prostaglandin	

## Sperm Number and Structure

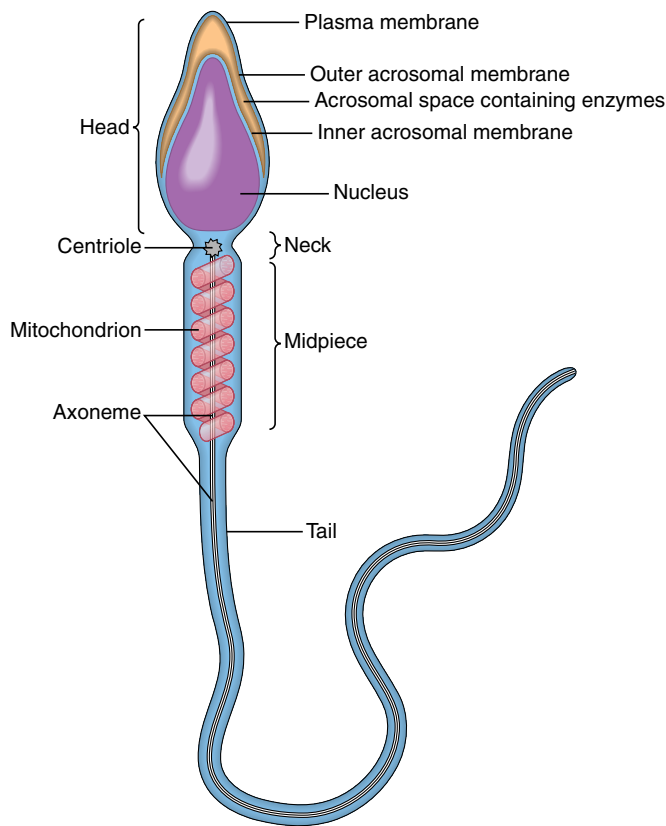
The number of sperm in a single ejaculate ranges from 40 million to 500 million (the average is about 182 million sperm). A male produces about 1 billion sperm (Fig. 9-1) for every ovum ovulated by a woman. Many ejaculated sperm (about 30%), however, are structurally or biochemically abnormal and are either dead or incapable of fertilizing; these are reabsorbed by the female reproductive tract or are lost through the vagina. For a male to be minimally fertile, his sperm count should be at least 20 million sperm/ml of semen; 40% of these sperm must swim and 60% should be of normal shape and size (Table 9-1).

Some evidence shows that human sperm count has declined over recent decades (see Chapter 4). One study suggests that the sperm count in healthy men has dropped 1% per year in the past 50 years. However, other studies contradict this idea, and whether there has been a worldwide decline in male fertility remains controversial. It is clear, however, that geographical differences in average sperm count exist. Differences in sperm production of men living in disparate regions of the world may reflect genetic, cultural, or environmental differences.

A healthy human sperm is 40 to 250  $\mu\text{m}$  long and is composed of the following structures (Fig. 9-2): neck, midpiece, and tail. The *sperm head* contains an elongated haploid nucleus surrounded by a nuclear membrane. External to the nucleus is a membrane-bound vesicle called the *acrosome*. It fits closely over the tip of the sperm head like a cap, and the *inner acrosomal membrane* lies external to the nuclear membrane while the *outer acrosomal membrane* is just inside the sperm cell *plasma membrane*. The acrosome is filled with enzymes important in the penetration of the ovum. The short sperm neck is followed by the sperm midpiece, which contains mitochondria that generate energy for tail movement. The midpiece and sperm tail represent a flagellum, with the “9 + 2” arrangement of microtubules. This provides the propulsive force, allowing locomotion of the sperm cell as it moves toward the egg and during egg penetration. A human sperm cell is 60–70  $\mu\text{m}$  in length.



**Figure 9-1** Photomicrograph of human sperm swimming in seminal fluid. The sperm heads shine because of a fluorescent dye.



**Figure 9-2** Sperm structure.

## Sperm Transport and Maturation in the Female Reproductive Tract

Let us now follow the sperm cells on their journey through the female reproductive tract to the point of fertilization in the oviduct, a distance of about 15 cm (6 in.). The sperm are first deposited in the vagina; they then pass up this cavity and through the cervix into the uterus, up the uterus, through the junction between the uterus and oviduct (uterotubal junction), and up the isthmus of the oviduct to the usual area of fertilization in the oviduct: the ampullary-isthmic junction. Many of the millions of deposited sperm are lost during this journey, and only about 100 to 1000 reach the oviduct, with 20 to 200 reaching the egg itself. In addition, the sperm must undergo maturational processes during their journey, which give them the capacity to move and to fertilize an ovum.

### Vaginal Sperm

About 1 min after deposition in the vagina, the semen becomes thicker and less liquid. This *semen coagulation* is brought about by the enzyme *fibrinogenase*



in the seminal plasma, which converts the protein *fibrinogen* to *fibrin*, another protein. The major function of this coagulation may be to prevent sperm loss from the vagina. After about 20 min, however, the semen again liquefies. This *semen liquefaction*, which is caused by a *fibrinolytic enzyme* in the seminal plasma, stimulates some sperm to swim more rapidly and to reach the cervix. Even though semen liquefaction has not yet occurred, some sperm make it into the cervix and even into the uterus within a few minutes of deposition in the vagina.

The environment in the vagina is usually acidic (about pH 4.2), and this level of acidity inhibits sperm motility. The presence of semen in the vagina, however, increases the vaginal pH to a basic 7.2, which in turn increases sperm motility.

During coitus, female orgasm is accompanied by muscular contractions of the vaginal walls (see Chapter 8), and these contractions create a pressure in the vagina that is higher than that in the uterus. Sperm movement through the cervix may be aided by this pressure differential. Sperm, however, can move up the female tract without female orgasm.

### Cervical Sperm

The cervical canal is lined by a complicated series of narrow folds and crypts and is blocked by a sticky mass of cervical mucus and tiny cervical fibers (see Chapter 3). In most stages of the menstrual cycle, the mucus is thick and fibers within it are densely packed. Shortly before ovulation, however, the rise in circulating estrogen levels causes the mucus to become more liquid and the gaps between the cervical fibers to widen. These gaps orient so that channels are formed. When the sperm enter the mucus, they line up in these channels almost in single file and pass through the cervix at a speed of about 1.2–3.0 mm per minute.

The cervical fibers may serve as a network upon which the sperm tails exert force, beating with a spiral motion and thus propelling the sperm upward. Also, these fibers may be of such dimension and length that they vibrate in rhythm with the tail beat frequency of normal sperm; this may allow normal sperm to move through the cervix, whereas sperm with abnormal or absent tail beats are detained. These latter sperm then die and are reabsorbed or lost from the body. Other sperm enter *cervical crypts* (deep recesses in the cervical wall), where they die or are lost, or they may remain alive as a reservoir of sperm that later may enter the uterus. Fewer than 1 million of the original 182 million sperm make it through the cervix.

### Uterine Sperm

Upon leaving the cervix, the sperm travel up the uterus to the uterotubal junction. The uterine fluid is watery but sparse in humans, and the sperm essentially “climb” up the uterine lumen by beating their tails. The swimming rate of sperm (about 3 mm/min), however, cannot account for their traveling a distance of about 15 cm in the 30 min after ejaculation. Also, dead sperm reach the oviduct at about the same time as do live sperm. Thus, sperm tail beating probably is not important during sperm transport through the uterus so it

must be the muscle contraction and movement of cilia in the female reproductive tract that facilitate sperm transport.

Mechanical stimulation of the cervix by the penis during coitus causes release of the hormone oxytocin from a woman's posterior pituitary gland. This hormone quickly travels via the blood to the uterus and increases the force of rhythmic uterine muscle contractions. These contractions act as waves to help the sperm move to the uterotubal junction. Prostaglandins in the seminal fluid may also cause uterine muscles to contract, but this is unlikely as very little if any seminal fluid enters the uterus through the cervix. The main function of the prostaglandins in seminal fluid is probably to contract the muscles of the vasa deferentia, thus aiding sperm passage during ejaculation.

The presence of sperm in the uterus initiates a massive invasion of white blood cells (*leukocytes*) into the uterine lumen. These cells then begin to engulf the dead or dying sperm that have not yet moved up to the uterotubal junction. No more than a few thousand sperm reach this junction.

The uterotubal junction is a muscular, tightly constricted region separating the uterus from the oviduct (see Chapter 2). Sperm enter the narrow opening of this junction and move through it at a relatively slow rate. Thus, the uterotubal junction allows the gradual entrance of sperm into the isthmus of the oviduct. About half of the sperm enter the wrong oviduct, and only a few hundred make it to the general proximity of the waiting egg.

## Transport of the Sperm and Ovum in the Oviduct

Sperm tail beating is reduced, and the sperm "wait" in the isthmus for ovulation to occur. Other sperm previously residing in cervical crypts are also released around the time of ovulation. After ovulation, several sperm move up to the ovum, and fertilization by a single sperm usually occurs at the point where the isthmus joins the wider oviductal ampulla (ampullary-isthmic junction). Other sperm swim up the ampulla, through the infundibulum, and are lost in the body cavity.

Once ovulation has occurred, the infundibulum (funnel-shaped free end) of the oviduct moves to the ovary and envelops the ovulated ovum along with fluid derived from the ovulated follicle. Movement of the infundibulum is accomplished by the contraction of muscles in the membrane supporting the oviduct. Cilia are present in the wall of the fimbria (the edge of the infundibulum) and these beat toward the uterus. Thus, when the infundibulum envelops the ovary, the beating of the cilia moves the ovum into the ampulla of the oviduct. Cilia in the ampulla and isthmus of the oviduct also beat in a uterine direction, which sets up a flow of fluid toward the uterus.

The muscles of the oviduct also exhibit waves of muscular contraction after ovulation. These waves travel in the direction of the uterus and, along with the cilia, help the ovum move down the oviduct. Both ciliary beating and muscular contraction in the oviduct are influenced by ovarian sex hormones. Estrogens increase cilia number, and progesterone increases ciliary beating and egg transport.

A factor involved in the opposite movement of egg and sperm may be the direction of ciliary beating in the oviduct. Oviductal cilia exist in deep recesses in which cilia beat toward the ovary and on ridges where these cilia beat

toward the uterus. Sperm may travel in these recesses, whereas the ovum may be propelled along the ridges. The presence of considerable amounts of mucus in the oviducts for 3 to 4 days after ovulation may serve as a medium for sperm transport. This mucus is gone when the fertilized ovum (embryo) travels down the oviduct to the uterus, as discussed in Chapter 10.

## Sperm Capacitation and Activation

Freshly ejaculated human sperm are not capable of fertilization. A period in the female reproductive tract is necessary before sperm can fertilize an oocyte. Thus, during their journey, sperm gain the ability to fertilize an egg (a process called *sperm capacitation*). *Calmodulin*, a protein in seminal plasma, may also play a role in sperm capacitation. This protein (or another epididymal secretion) may give the sperm the ability to be capacitated later on when they are in the uterus.

In general, the present scientific opinion is that capacitation involves removal or modification of molecules (glycoproteins) associated with the sperm head that stabilize the sperm plasma membrane. These molecules suppress the ability of sperm to fertilize. Alteration or removal of these inhibitory molecules allows the sperm to respond to signals that trigger the acrosome reaction, an important step in the fertilization process. Capacitation also increases the vigor or tail movements of the sperm (*hyperactivation*), propelling it toward the egg more effectively.

What substances in the female reproductive tract render the sperm capable of fertilization? One possibility is that molecules in follicular fluid escaping from the ovulating follicle play a role in sperm capacitation. Follicular fluid contributes only a small part of the oviductal fluid. Studies of mammals have demonstrated that two components of follicular fluid, progesterone and the protein albumin, facilitate the acrosome reaction. Calcium in follicular fluid increases the vigor of sperm tail beating. It is not clear if these substances are present in humans, although follicular fluid does activate human sperm. If operative in humans, they may have their effect when the sperm penetrates the cumulus oophorus (see later), which surrounds the ovum and is bathed in follicular fluid. A recent discovery is that follicular fluid, or the egg itself, produces a chemical that attracts human sperm (see HIGHLIGHT box 9-1). Another study suggests that mammalian sperm move toward the egg along a thermal gradient. The site of fertilization is slightly warmer than more proximal portions of the oviduct, and mature sperm have a preference for moving toward warmer fluid (*thermotaxis*). Sperm may be guided by temperature during most of their journey through the fallopian tube and then respond to chemical cues as they near the egg. In the future, we may expand our concept of sperm capacitation to include acquisition of the ability to detect chemical and/or thermal cues.

## When Can Fertilization Occur?

Most references state that sperm live about 72 h and that an egg is fertilizable for 24 to 48 h. Thus, the fertile time in a menstrual cycle would be about 4 to 5 days,

## Chapter 9, Box 1: Does the Human Egg Court Sperm?

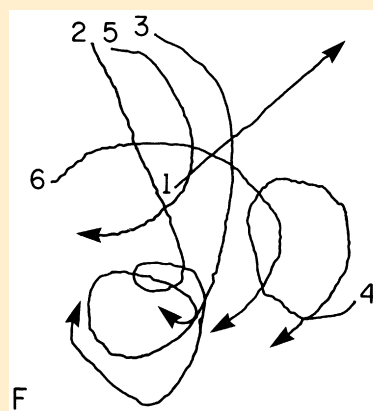
Out of the millions of sperm deposited in the vagina during ejaculation, only 20 to 200 will reach close proximity to the egg in the oviduct, and yet the competition among sperm to be the one that fertilizes the ovulated egg is not finished. Part of the future of a sperm (to become part of a new embryo or to die as a haploid failure) could depend on its response to "courtship" by the egg and/or its surrounding fluid.

The sperm of algae, mosses, ferns, and some invertebrate animals are attracted to the egg chemically, but until recently only one case of such attraction has been described in a vertebrate animal. The egg of the herring (a teleost fish) is covered by a zona pellucida-like coat (the "chorion"), and the chorion cannot be penetrated by sperm swimming in the surrounding water unless it locates a small opening in it. This opening, the micropyle, secretes a chemical that activates and attracts sperm to it. However, until recently, there had been no evidence that the human egg attracts sperm. The prevailing theory had been that the human sperm present in the vicinity of the egg bump into it by chance.

A new finding, however, suggests that the human egg produces a chemical that attracts sperm and influences their swimming motion. If follicular fluid from a large graafian follicle is placed at one end of a chamber, sperm will accumulate at that end, whereas they will not respond to a control fluid. The quantities of estradiol or progesterone in the fluid do not influence this response, but only some and not all follicles have fluid that works. A good correlation also exists between the fertilizability of an egg and the ability of its surrounding fluid to attract sperm. Control fluid previously containing an egg also attracts sperm, so it appears that this signal comes from the egg, not the surrounding follicular cells.

When sperm are exposed to the egg signal, they swim in a circle instead of in a straight

line, which would increase their chances of contacting the egg. Interestingly, not all sperm are attracted to the egg; some could care less and some even swim away from the egg! A human sperm has about 20 chemical receptor molecules on its head, and maybe some sperm have not formed the receptor(s) used in this chemical orientation to the egg or perhaps they are abnormal in other ways. Nevertheless, they will not be the chosen one! Many questions still remain. What is the chemical that attracts sperm? Why do some eggs produce the chemical and some not? Why do some sperm respond whereas others do not? Does the chemical cause more sperm to move up the oviduct leading to the egg instead of the "empty" oviduct? Do X and Y sperm behave differently in response to this chemical? Could an inhibitor of this chemical be used as a new contraceptive agent? Only time will tell.



Six human sperm were placed in a fluid-filled chamber. Their starting position is represented by the numbers 1 through 6. Then, either follicular fluid from a human Graafian follicle or fluid exposed to a human egg was injected at the lower left-hand corner (F). Arrowed lines then indicate the path swum by each sperm. Note that sperm 2 through 6 turned and headed toward F. Sperm number 1, however, was not interested. (Adapted from Ralt *et al.* (1991).)

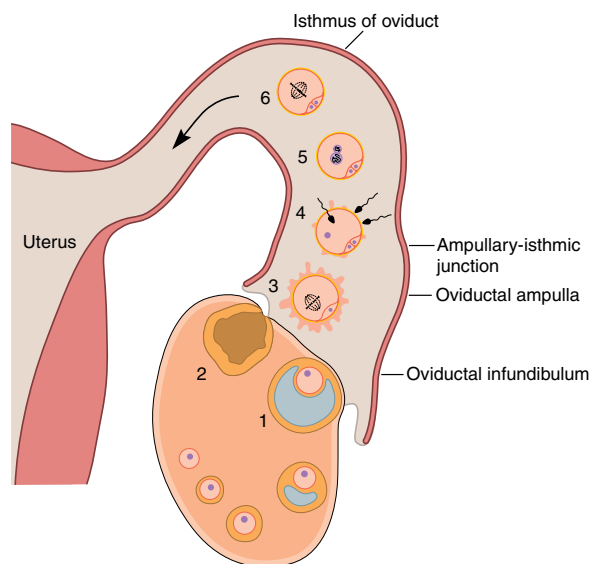
with ovulation occurring at about the middle of this time period. A recent study, however, has cast suspicion on this theory. This study found that conception can only occur in a 6-day period, i.e., during the 5 days before ovulation or on the day of ovulation. Therefore, some sperm live for 6 days and the egg lasts 12 to 24 h (or the change in cervical mucus after ovulation halts sperm transport).

## The Process of Fertilization

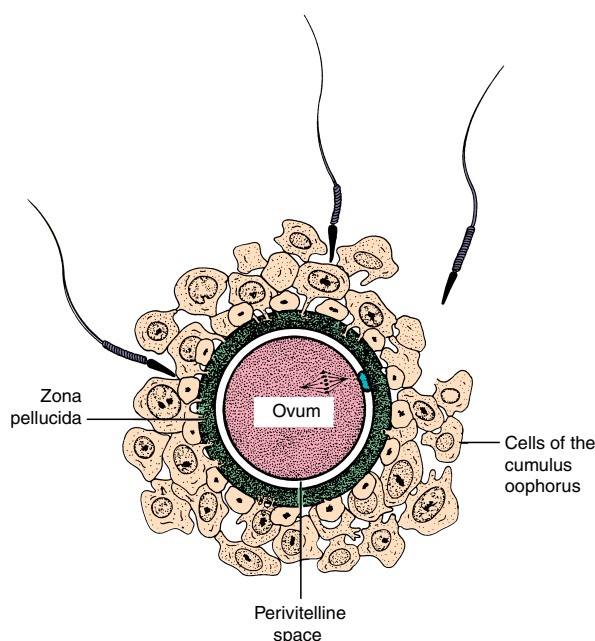
Once a sperm and ovum are in the region of the ampullary–isthmic junction of the oviduct (Fig. 9-3), fertilization occurs. In the fertilization process, a sperm first penetrates between the cells constituting the cumulus oophorus and then through the zona pellucida and into the perivitelline space. The sperm then enters the oocyte through its cell membrane (the *vitelline membrane*). The following is a discussion of what happens during each of these processes, and Figs. 9-4 and 9-5 depict these processes. The entire process of fertilization takes about 24 h.

### Sperm Passage through the Cumulus Oophorus

The ovulated ovum is surrounded by the cumulus oophorus, which is a sphere of loosely packed follicle cells (Fig. 9-4). Appropriately, cumulus oophorus means “egg-bearing little cloud.” As a sperm enters the cumulus oophorus, the enzyme *hyaluronidase* on the sperm head dissolves hyaluronic acid, a major component of the cementing material found between the cells of the cumulus oophorus as well as between other cells in the body. Enzymatic dissolution of hyaluronic acid allows the swimming sperm to penetrate the cumulus oophorus and to reach the zona pellucida.



**Figure 9-3** Diagram of the human ovary, oviduct, and part of the uterus showing fertilization: (1) Follicle in ovary is ready to ovulate; (2) new corpus luteum; (3) ovulated ovum is arrested in second meiotic division (note the first polar body); (4) formation of second polar body after fertilization; (5) fusion of egg and sperm pronuclei; and (6) beginning of first mitotic division of zygote.



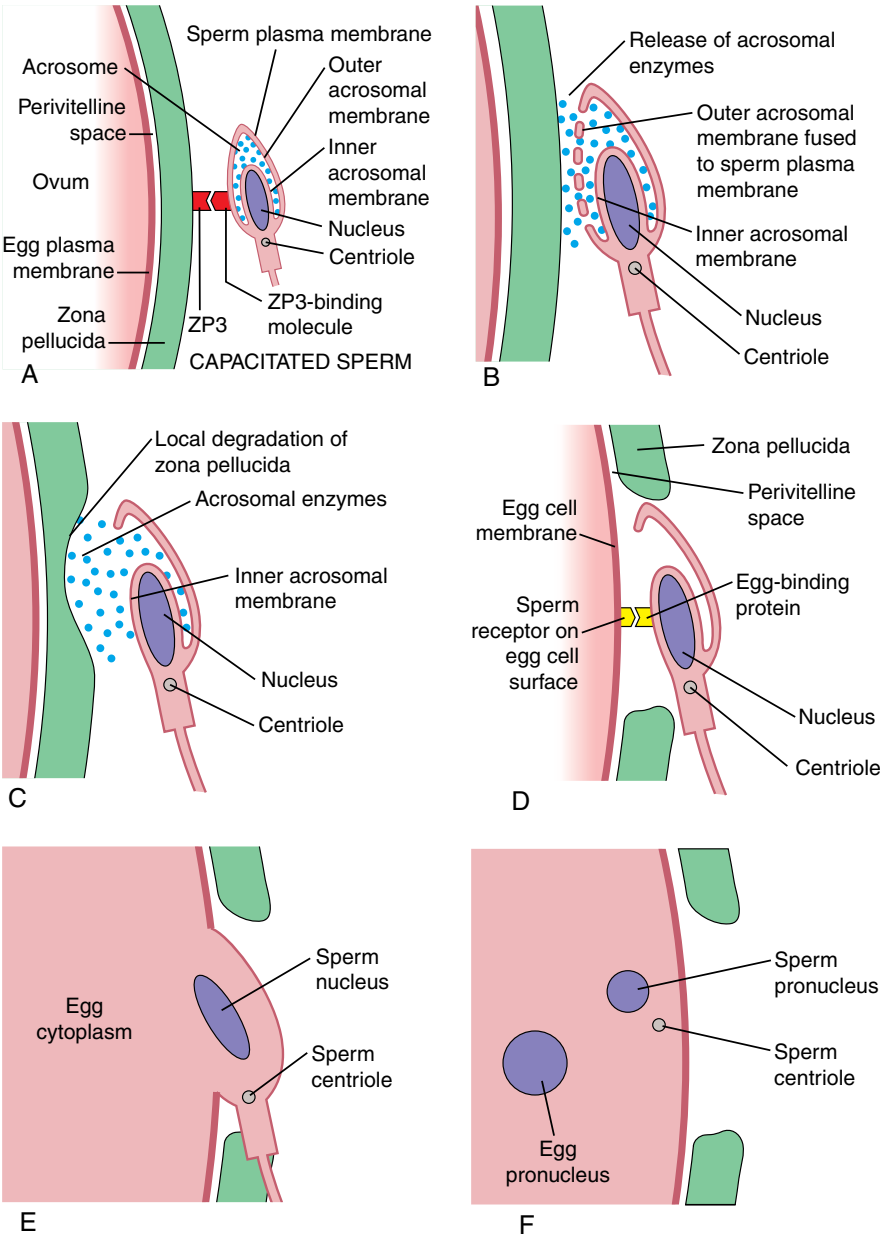
**Figure 9-4** Illustration of the barriers around the recently ovulated ovum through which the capacitated sperm must pass to reach the perivitelline space and achieve activation and fertilization of the ovum.

### *Sperm Passage through the Zona Pellucida*

The zona pellucida is an extracellular matrix composed of three glycoproteins termed ZP1, ZP2, and ZP3. Receptors on the sperm plasma membrane attach to ZP3. This ZP3 receptor binding allows the sperm to adhere to the zona pellucida and is a critical step in fertilization. It triggers the sperm head to undergo the *acrosome reaction*. An influx of calcium and a rise in pH and cAMP levels within the sperm head cause exocytosis of the acrosomal vesicle. That is, the plasma membrane of the sperm fuses with the outer acrosomal membrane, forming many small openings to the acrosome. Contents of the acrosome, which are hydrolytic enzymes, spill out and degrade the zona pellucida near the sperm head. This forms a tunnel in the zona, through which the sperm begins to move (Fig. 9-5).

Degradation of the sperm plasma membrane causes the loss of ZP3 receptors. However, now the inner acrosomal membrane is exposed, and it appears to have receptors for another zona pellucida glycoprotein called ZP2. This ZP2 binding maintains the contact between egg and sperm. The sperm tail continues to beat vigorously, helping the sperm penetrate through the zona pellucida and make contact with the plasma membrane of the egg. Once the sperm has penetrated the zona pellucida, it moves through a narrow, oblique path into the *perivitelline space* (the area between the zona pellucida and the vitelline membrane, see Fig. 9-4). Penetration of the human zona pellucida by a sperm takes less than 10 min under experimental conditions.





**Figure 9-5** Stages of fertilization. Capacitated sperm have already passed through the cumulus oophorus surrounding the egg; for clarity, cumulus cells are not shown. (a) Proteins on the sperm plasma membrane bind to ZP3 molecules within the zona pellucida of the egg. (b) Zona binding triggers the acrosome reaction, in which the sperm plasma membrane fuses with the outer acrosomal membrane, causing exocytosis of acrosomal contents. (c) Acrosomal enzymes begin to dissolve a hole in the zona pellucida. This enzymatic degradation, accompanied by rapid sperm tail beating, moves the sperm through the zona. (d) Egg-binding proteins on the sperm cell surface bind to molecules on the egg cell membrane. (e) The sperm cell membrane fuses with the egg plasma membrane, allowing the sperm nucleus and centriole to enter the egg cytoplasm. (f) Egg and sperm pronuclei migrate toward each other in preparation for syngamy.

### ***Sperm Attachment to the Egg Plasma Membrane***

The sperm approaches the egg sideways instead of head on, and the sperm head now lies parallel to the egg cell surface within the narrow perivitelline space (Fig. 9-5). At this point, the posterior part of the sperm head attaches to the egg plasma membrane. The plasma membranes of sperm and ovum fuse, forming an opening into which the sperm nucleus, midpiece, and most of the tail sink into the egg cytoplasm. Scientists are actively investigating the molecules involved in egg-sperm adhesion and subsequent fusion. Finding the molecular basis of sperm-egg fusion may help us understand certain forms of infertility and could possibly lead to new contraceptives.

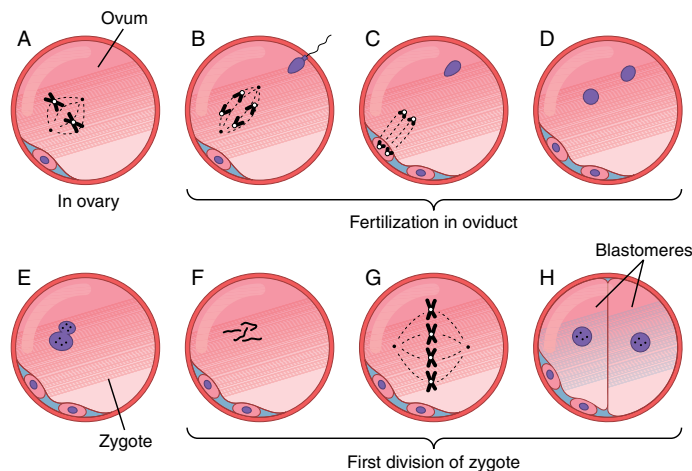
### ***The Cortical Reaction***

Once a sperm has entered the egg, it is imperative that no other sperm be permitted to fertilize it. If additional sperm were allowed to enter the egg, the extra genetic material they carry would disrupt normal development, and the resulting polyploid embryo would die. To prevent *polyspermy* (fertilization by more than one sperm), the egg now mounts a defense. Just underneath the plasma membrane of the egg lie small, membrane-bound vesicles called *cortical granules*. At fertilization, there is a sudden, dramatic burst in available free calcium in the egg cytoplasm as it is released from cytoplasmic storage. The rise in calcium causes cortical granule membranes to fuse with the adjacent cell membrane. Thus, the cortical granules open to the exterior and release their contents into the perivitelline space. Included in the cortical granule contents are enzymes that act on constituents of the zona pellucida. These enzymes alter ZP2 and ZP3, destroying their receptor sites for the sperm head. Thus, no additional sperm can attach to the zona pellucida to gain access to the egg.

The cortical reaction is the first step in a series of biochemical and physical changes in the egg known as *egg activation*. These rapid changes begin just after fertilization and are preparations for early embryonic development. In addition to the cortical reaction, egg activation involves completion of meiosis, increase in egg metabolism, synthesis of protein, RNA, and DNA, and preparation for the first mitotic division. All of these essential first steps in development are dependent on the initial rise in free calcium. We do not know exactly how fertilization initiates a calcium rise in the egg. One theory (the *receptor hypothesis*) suggests that binding of a sperm to an egg receptor induces biochemical changes in the egg cytoplasm that cause release of stored calcium. An alternative idea (the *cytoplasmic factor hypothesis*) is that as the sperm enters the egg cytoplasm, it carries a factor that causes free calcium to be released. Laboratory experiments lend support for each of these hypotheses, but the actual mechanism that occurs during normal fertilization remains unknown.

### ***Completion of the Second Meiotic Division***

The ovulated egg is arrested in the second meiotic division and still has a duplicated set of chromosomes. Before merging with sperm DNA, the egg must complete its second meiotic division and jettison one set of its chromosomes.



**Figure 9-6** The nucleus of the ovulated egg is haploid and its chromosomes are arrested in the second meiotic division (1). The first polar body may divide into two small cells (1), one of which is pictured in further figures. Sperm penetration activates the egg so that the second meiotic division is completed (2, 3) and a second polar body is formed (4). The egg and sperm pronuclei then fuse (5) and the resultant diploid zygote now divides mitotically (6, 7) to form a two-cell embryo (8) consisting of two blastomeres. Note that only two chromosomes are shown in (1), even though there should be 23.

At fertilization, the rise in free calcium activates the egg nucleus to complete meiosis, and a second polar body is produced, removing the extra set of chromosomes from the egg. The second polar body can often be seen in the perivitelline space before it degenerates (Fig. 9-6).

### Formation and Fusion of Sperm and Egg Pronuclei

Soon after the sperm nucleus enters the egg, its nuclear membrane breaks down. The sperm DNA decondenses as a result of exposure to factors in the egg cytoplasm. A new membrane then forms to enclose the *sperm pronucleus*. Sperm and egg pronuclei begin to migrate toward each other, replicating their DNA as they move. As they approach each other, their nuclear membranes break down and the two duplicated sets of chromosomes aggregate. Syngamy (merging of the two haploid genomes) has now occurred, and the fertilized egg (*zygote*) is the beginning of a new individual. In mammals, it takes about 12 h from the beginning of egg activation to pronuclear fusion. The centrosome contributed by the sperm organizes a mitotic spindle, and chromosomes now begin to line up at the metaphase plate. The zygote next divides mitotically, and two identical daughter cells, termed blastomeres, are formed (Fig. 9-6). Embryonic development has commenced.

We have seen that the sperm contributes its haploid chromosomes and centrosome to the zygote. The sperm tail disintegrates in the egg cytoplasm. What happens to the sperm mitochondria? It has long been known that the approximately 100 mitochondria brought by each sperm into an egg disappear soon after fertilization. Recent studies have demonstrated how this occurs. During spermatogenesis, sperm mitochondria are tagged with a protein called *ubiquitin*, a molecule

used by all cells to mark proteins slated for destruction. These tagged paternal mitochondria are then destroyed and recycled by the egg after fertilization. Thus, all of our mitochondria are inherited from our mothers. Maternal inheritance of DNA-containing mitochondria has been a useful way to trace human origins.

## Chapter 9, Box 2: Sperm Hitchhikers

Deprived of all but a scant amount of cytoplasm during the latter stages of spermatogenesis, the human sperm has, until recently, been considered to contribute nothing to the ovum except for its nuclear DNA and centriole. However, we know that factors carried by the sperm play active roles in the fertilization process. Some men with sperm apparently normal in shape, motility, and abundance still are infertile if they lack these biochemical factors. From the text, you know that some of these factors are enzymes such as hyaluronidase and acrosomal, enzymes necessary to break through the layers of cumulus cells and the zona pellucida before reaching the egg surface. Also necessary are zona-binding proteins on the surface of the sperm cell membrane and inner acrosomal membrane. However, these are not all of the players in the process of fertilization, and some sperm "hitchhikers" may also be important for normal development of the egg and embryo.

For example, the sperm head contains a protein, *fertilin-β*, on its surface. After the sperm penetrates the zona pellucida, the tip of its head approaches the vitelline membrane. Then the head turns laterally so that one side of the sperm head attaches to the vitelline membrane (see text). *Fertilinβ* appears to mediate this lateral attachment. If this protein is absent, fertilization does not occur because sperm–oocyte binding is inhibited. *Fertilin*-deficient sperm also have a reduced ability to bind to the zona, and our understanding of the normal action of *fertilin* is still evolving.

When the sperm penetrates the egg, waves of stored calcium ions are released in the egg cytoplasm. This sudden increase in calcium triggers egg activation (cortical granule release and reinitiation of meiosis). Scientists have long speculated that the trigger for calcium release is carried by the sperm.

Researchers have found that the sea urchin sperm head contains an enzyme that can synthesize *nitric oxide*. This gas is injected into the egg at fertilization and can set off a calcium surge. It remains to be seen if a similar mechanism operates in humans. Study of human eggs has revealed that *phospholipase C* is carried by sperm into the egg. It also can cause the waves of calcium release and egg activation.

*Ribonucleic acid* (RNA) is produced when cells read the DNA sequences coded by the genes and transcribe these messages. During the later stages of spermatogenesis, sperm DNA becomes tightly compressed and gene expression ceases. However, scientists have found that sperm RNA is still present in the mature sperm even at fertilization. This is especially surprising because the sperm cytoplasm is virtually gone. Sperm cells contain an amazing repertoire of RNAs. It turns out that about 3000 of the 20,000–25,000 human genes are represented by sperm RNA. Some of the mRNAs represent known genes, others are unknown, and some of the RNAs do not code for proteins. Many types of mRNAs are found in the sperm cell nucleus.

Most of these 3000 transcripts are probably leftover RNA instructions for building the sperm cell during the process of spermatogenesis. However, scientists have identified six RNAs present in the spermatozoa but not in the unfertilized egg. They then asked if these transcripts are carried into the egg at fertilization. If the sperm delivers RNAs into the egg at fertilization, one would expect to find these RNA sequences in the sperm and in the zygote, but not in the unfertilized egg. Using cDNA probes, they found two sperm RNA sequences that are delivered to the egg at fertilization.

What happens to RNAs delivered by the sperm? Possibly they are simply destroyed by

*Continued on next page.*

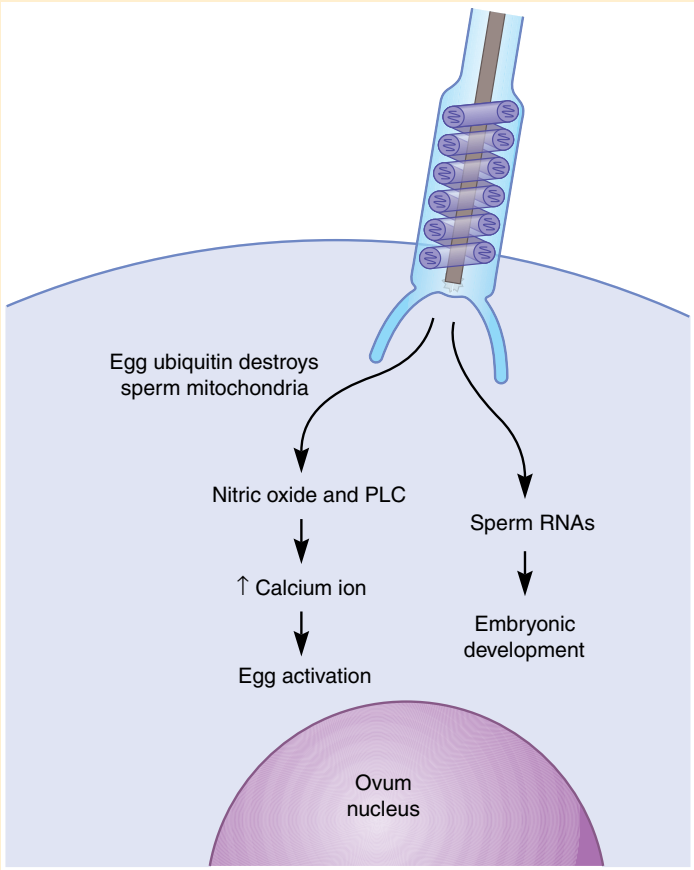
Chapter 9, Box 2 continued.

the egg cytoplasm. However, it is also possible that these RNAs act as instructions for early embryonic development and that they are needed to launch the developmental program of the zygote. In fact, one of the mRNA transcripts delivered to the egg codes for *clusterin*, which has been implicated in cell–cell interactions, membrane recycling, and regulation of apoptosis (programmed cell death), processes central to embryonic development.

Preliminary evidence shows that the sperm of some infertile men lack some of the RNAs carried by sperm of fertile men. In fact, it is thought that a treatment that lowers or eliminates the RNAs from the sperm of fertile men may render them infertile, thus providing a

potential male contraceptive method. Some scientists use the absence of male RNAs as a possible explanation of why embryonic development is so poor in most cases of cloning and in all cases of human parthenogenesis; neither process involves sperm. However, others cite the occasional success of cloning to argue against an important role for sperm RNAs.

As new sperm molecules are discovered, the role of the sperm has expanded from simply delivering a haploid genome to the egg to essential roles in the fertilization process and perhaps important roles in egg activation and early embryonic development as well.



Possible influences of the sperm cell on the egg and/or early embryo in addition to the contribution of its haploid nucleus. For clarity, the sperm cell is shown oriented at right angles to the egg cytoplasm.

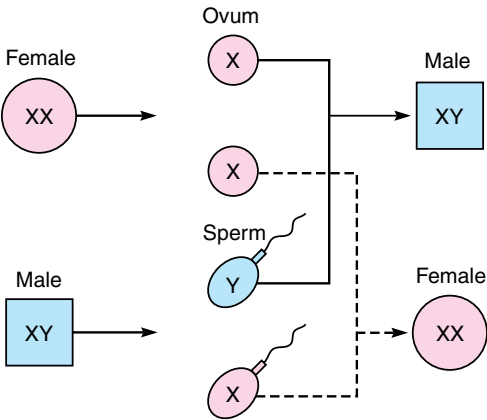
Chemical Inhibition of Fertilization

In the future, it may be possible to block fertilization by interfering with steps in the fertilization process. A search for vaccinations against sperm, egg, or the early embryo has long been underway. More recently, studies have focused on specific ways to thwart the actions of sperm cells, either by immobilizing them or by preventing them from undergoing the acrosome reaction, binding to the zona pellucida, or fusing with the egg cell membrane. Some of these potential future contraceptive methods are discussed in Chapter 14.

Sex Ratios

As discussed in Chapter 5, the normal chromosome number in humans is 46 (2N, diploid). Females have 22 pairs of autosomes and two X chromosomes. Males have 22 pairs of autosomes and an X and Y chromosome. The genes for male sex determination are carried on the Y chromosome. Thus, embryos without a Y chromosome are female.

As a result of meiosis in the adult testis, one diploid male germ cell (spermatogonium) gives rise to four haploid spermatozoa (see Chapter 4). Two of these spermatozoa will have 22 autosomes and a Y chromosome, whereas the other two will have 22 autosomes and an X chromosome. If a Y-bearing sperm (22Y) fertilizes an ovum (with 22 autosomes and an X chromosome), the embryo will be male; if an X-bearing sperm (22X) fertilizes an ovum, the offspring will be female. Thus, given an equal chance of X and Y sperm to fertilize, the sex ratio of embryos should be 100:100 (Fig. 9-7). However, the ratio of male to female embryos at conception (the *primary sex ratio*) is about 120:100. This ratio is based on the sexes of early aborted embryos. It is assumed that this means a greater fertilization rate by Y sperm than X sperm, perhaps because Y sperm are lighter and faster swimmers than X sperm.



**Figure 9-7** The chromosomal basis for the existence of an equal number of X and Y sperm, and thus a theoretical primary sex ratio of 100:100. As discussed in the text, this theoretical ratio is not borne out, and more embryos are male than female.



However, female embryos may die more frequently at an earlier age than male embryos or more X sperm may die in the female reproductive tract than Y sperm. The sex ratio of male births to female births (the *secondary sex ratio*) is 105:100. Thus, for reasons not yet understood, male fetuses suffer a greater mortality than female fetuses in the uterus.

## Sex Preselection

Couples who desire to choose the sex of their baby may now do so. A relatively new technology (the *microsort method*) is the most effective procedure yet devised at separating X-bearing and Y-bearing sperm. It takes advantage of the fact that the large X chromosome has considerably more DNA than the tiny Y chromosome. A sperm sample is first collected from the prospective father. Then, the sperm cells are treated with a fluorescent dye that attaches to DNA and glows under laser light. Sperm with more DNA, scientists reasoned, would glow more brightly. Although X sperm have only 2.8% more DNA than those carrying a Y chromosome, the difference in brightness is sufficient to be distinguished by a light detector. The tagged sperm are sent through a very narrow tube with a diameter wide enough to allow only one sperm cell at a time. As sperm move through the tube, they are illuminated by a laser beam. An automated mechanical sperm sorter then separates the sperm, sending X sperm down one tube and Y sperm into another. The sorted sperm can then be placed in the woman's uterus (artificial fertilization) or used for *in vitro* fertilization. Approximately 91% of sperm cells in the X-bearing tube contain an X chromosome. This procedure is only about 74% effective in selecting Y-bearing sperm. Thus, the results are not foolproof, but this method does improve the chances of producing an embryo of the desired sex, especially if a couple wishes to have a girl.

A more accurate method of ensuring the sex of a baby is *preimplantation genetic diagnosis (PGD)*, which is available at a limited number of clinics. It involves *in vitro* fertilization followed by embryo selection. The mother's eggs and father's sperm are collected, and the eggs are fertilized in the laboratory. After 3 days of development, a cell is carefully removed from each embryo and chromosomes are examined. Those carrying a Y chromosome are separated from non-Y-bearing embryos. Only embryos of the desired sex are implanted into the mother's uterus. Although nearly 100% accurate, this procedure is more invasive, expensive, and controversial than sperm-sorting techniques.

Why would parents wish to preselect the sex of their offspring? One reason would be to avoid sex-linked genetic diseases, which are more likely to occur in males. Parents may also wish to balance their families or they may simply prefer to have a child of a given sex. Some have expressed concerns that the ability to select a baby's sex may be the first step to "designer children" chosen for other traits such as height, IQ, athletic, or musical ability. Others fear that widespread sex selection would lead to a gender imbalance in society and cause social problems. In fact, a preference for baby boys in China has led to a significant shift in the sex ratio in some areas of the country. In such cultures where boys are valued more highly than girls, the ability to select sex before fertilization could avoid costly and ethically controversial practices such as amniocentesis (genetic screening for sex), selective abortion, and even infanticide. In the United States, sperm selection likely would not lead to overall gender imbalance, as family preference

for a girl or a boy baby is split more evenly. Finally, the ability to preselect a child's sex may help families limit their size. For example, using gender selection technology, a family with three boys could increase their likelihood of having a girl as their fourth and last child instead of continuing to have babies until a girl was conceived. However, the present high cost of the microsort and PGD methods likely will limit the practice of sex preselection in the foreseeable future.

## Multiple Embryos

Twins occur in about 1 of every 80 or 90 pregnancies. When two ova are released and each is fertilized by a different sperm, *fraternal twins* are produced. These twins are *dizygotic* (the products of two different zygotes) and can be the same or different sex. Fraternal twins, which are *nonidentical* and are as different from each other as are nontwin brothers and sisters, account for two-thirds of all twins. The incidence of dizygotic twins is influenced by race and by inherited factors from the mother (not the father). Fraternal twins are more common in older mothers.

*Identical twins*, which are rarer than fraternal twins, usually occur when an early embryo divides into two. These twins are *monozygotic* (derived from one zygote) and are identical genetically. The incidence of identical twins is not related to race, inheritance, or age of the mother. Rarely, identical twins are *conjoined* (i.e., they fail to separate completely during embryonic development). These are called *Siamese twins*, after the first publicized Siamese twins, “Chang” and “Eng” (1811–1874), born in Siam of Chinese extraction. They were united at the chest by a thick mass of flesh. Some Siamese twins have been separated surgically after birth. For more on twin pregnancies, see Chapter 10.

When the number of embryos is greater than two (e.g., triplets, quadruplets), all are usually of multizygotic origin; in a few cases, some are multizygotic and some are monozygotic.

## Parthenogenesis

Is it possible that an embryo can develop in a human female without previous fertilization? Embryonic development from an ovum not previously stimulated or penetrated by a sperm is called *parthenogenesis*. Such “virgin birth” is common in many insects, in some fish, amphibians, and reptiles, and in a strain of domestic turkeys. In addition, parthenogenetic mouse embryos can be produced in the laboratory, but they do not develop to term. There is no proven case of a parthenogenetic birth in humans. If parthenogenesis could occur, reduction division in the oocyte must not occur, the offspring would always be female, and the child would be genetically identical to the mother.

## Chromosomal Aberrations

Errors of meiosis or fertilization can produce embryos with chromosomal aberrations. More than 90% of these embryos are aborted spontaneously, usually within the first trimester. In fact, 42% of embryos or fetuses that are

aborted spontaneously have chromosomal abnormalities. A few fetuses with chromosomal defects, however, are born; about 1 out of every 100 newborns has such a defect. It must be emphasized that some of these disorders are not inherited in the strictest sense because the genes of the parents do not govern their occurrence.

In rare cases, one sperm will fertilize the ovum and a second sperm will fertilize the polar body. The two fertilized cells then form an embryo that is a genetic mosaic in that half of its cells will have a different genetic makeup from the other half. This condition also can occur when the haploid ovum divides into two cells and each cell is then fertilized by a separate sperm. If an X and a Y sperm were involved, half of the cells of an embryo would be male and half female, resulting in an intersex (see Chapter 5).

One kind of chromosomal aberration occurs when fertilization fails to activate the second meiotic division in the ovum. Thus, there is no egg pronucleus and the embryo develops with only one set of chromosomes (haploid) and genes of the male only. This process of embryonic formation is termed *androgenesis*. A similar situation occurs when the ovum pronucleus develops normally, but the sperm pronucleus does not form. In this case, called *gynogenesis*, the embryo also is haploid but has only the female's genes. Both of these conditions are lethal after only a few cell divisions in the embryo.

In contrast to the previously mentioned conditions, some embryos may develop with triploid cells (3N) that have 69 chromosomes (three complete sets). *Triploidy* can occur in at least three ways. First, sperm penetrating the ovum may be the product of a failure of reduction division during meiosis in the testis, and thus it has 46 instead of the normal 23 chromosomes. When this sperm fertilizes a haploid ovum, a triploid embryo develops. Second, even though mechanisms to prevent polyspermy are present, these mechanisms are not fail-safe. Thus, two haploid sperm can penetrate a single ovum (polyspermy) and both of their pronuclei then fuse with the haploid ovum pronucleus. Finally, reduction division (meiosis) may not have occurred in the oocyte, and the resultant diploid female pronucleus then fuses with a haploid sperm pronucleus to produce a triploid zygote.

The excess dosage of genes in triploid embryos tends to be less destructive than when there are too few genes, as in androgenesis or gynogenesis. Most triploid embryos develop to about the third month of pregnancy before aborting spontaneously. The very few triploid fetuses that survive to term are malformed and are stillborn or die soon after birth. Less than 1% of all human embryos are triploid.

Another error in fertilization results in embryos with either one too many (47) or one too few (45) chromosomes in their cells; these conditions are collectively called *aneuploidy*. This happens when there is aberrant chromosome movement during the first or second meiotic division in the testis or ovary or in the first cleavage division of the zygote. That is, a pair of chromosomes fails to separate during division, with both members going to one daughter cell (*nondisjunction*). The resultant cell has 47 chromosomes, and the cell coming up short has only 45. Thus, the aneuploid condition can be either *monosomic* (45 chromosomes) or *trisomic* (47 chromosomes).

Most monosomic embryos abort spontaneously early in their development. An exception, however, is when monosomy for a sex chromosome occurs. That is, each cell has only a single sex chromosome, either an X or a Y. About 98% of

these embryos abort, but a few with one X (XO condition; Turner's syndrome) are born as sterile females with short stature and physical defects (see Chapter 5). Only 1 in 3500 living females has this syndrome.

Most trisomic embryos die in the second or third month of pregnancy and abort spontaneously; 20% of miscarried fetuses are trisomic. Some, however, are born with severe physical and mental defects. The most common trisomic condition in infants is *Down syndrome*, also called *Mongolism*, a condition in which the cells of the individual are trisomic for chromosome number 21. Children with Down syndrome exhibit abnormal body development and severe mental retardation.

For some as yet unknown reasons, the gametes of older men and women are more likely to produce trisomic embryos. The chances are 1 in 1000 for having a trisomic embryo for women under 35, but are 1 in 200 for 35-year-old women and 1 in 15 for 45-year-old women. Women over 35 have 15% of all babies but 50% of all Down's syndrome children. Therefore, it is recommended that women in their midthirties consider having the cells of their fetus examined by amniocentesis or chorionic villus biopsy (see Chapter 10) for evidence of chromosomal abnormalities. If certain chromosomal aberrations are found, induced abortion might be considered (see Chapter 15). It used to be thought that errors in meiosis in oocytes of older women were the main cause of trisomy. Recently, however, we have become aware that about one-fifth of trisomic infants are caused by chromosomal abnormalities in the sperm of older men.

As discussed in Chapter 5, nondisjunction of sex chromosomes can produce males with trisomic cells of an XXY or XYY makeup. In the former condition, Klinefelter's syndrome, males are sterile and have female-like breasts. About 1 out of 600 males is born with this condition. In the latter "supermale" condition (XYY), males are very tall and often have acne. These males tend to exhibit mental and social adjustment problems at a higher percentage than normal XY males. One in 2000 males has XYY cells. Some statistical evidence exists that the percentage of XYY males (1.8 to 12.0%) in penal institutions is greater than their percentage (0.14 to 0.38%) in the general population. Some controversy, however, surrounds these studies and it is not clear if the greater maladaptive behavior of XYY males is a direct result of their chromosomal abnormality or is due to social problems they had when growing up because of their unusual physical appearance. Apparently the elevated crime rate of XYY men is not related to aggression but may be related to low intelligence. Women with nondisjunction of the X chromosome have cells that are XXX. These women are female but sterile. Cases in which males have several X chromosomes (XXXY) are due to penetration of the ovum by more than one sperm.

Sometimes a gamete contains a chromosome with an extra piece from another chromosome attached to it; this is the result of *chromosomal translocation*. The chromosome from which the piece was taken thus suffers from *chromosomal deletion*. An example of a disorder resulting from chromosomal deletion is the *cri du chat* (French for "cry of the cat") syndrome, in which a piece of chromosome 5 is missing. These children are born with a small head, widely separated eyes, low-set ears, and mental retardation. When they cry, it sounds like a hungry kitten. Human kidney cancer has also been linked to an inherited chromosomal translocation in which a piece of chromosome 3 is hooked onto chromosome 8.

An inherited disorder of the X chromosome (*fragile X syndrome*) is the second leading cause of mental retardation. In these people, the X chromosome (in either sex) has an abnormally long, fragile arm. In this disorder, mental retardation is less severe in females than in males.

## Chapter Summary

After sperm mature in the epididymides, they move down the vasa deferentia. Seminal plasma consists of secretions from male sex accessory glands. These secretions are added to the sperm to form semen (seminal fluid), which leaves the male urethra during ejaculation. Seminal plasma contains substances necessary for sperm movement, maturation, and maintenance.

About 66 million sperm are present in each milliliter of semen. Some of these sperm are abnormal and die. A healthy sperm is made up of a head (nucleus plus acrosome), neck, midpiece, and tail. After insemination of the female, the sperm move through the vagina, cervix, uterus, and into the oviduct. While in the uterus and oviduct, sperm acquire the ability to fertilize (capacitation) and are activated so that their tails beat more rapidly. Meanwhile, the ovulated ovum moves down the oviduct, and the sperm and ovum meet at the ampullary-isthmic junction of the oviduct, where fertilization occurs.

Before penetrating the ovum, a sperm moves first through the cumulus oophorus and zona pellucida. As it binds to the ZP3 glycoprotein on the zona pellucida, it undergoes the acrosome reaction, during which the sperm acrosome releases enzymes that help dissolve the zona. Once the sperm enters the ovum, it causes the completion of oocyte meiosis and the cortical reaction, which produces changes in the zona pellucida that act as a barrier to polyspermy. The haploid sperm pronucleus and egg pronucleus then merge, and a zygote is formed. In the future, certain chemicals may be used to block fertilization as a method of birth control.

Chromosomal sex is determined at fertilization, and couples may now be able to choose their baby's sex. Identical twins (monozygotic twins) are formed when a single sperm fertilizes a single ovum, after which the embryo divides into two. Fraternal twins (dizygotic twins) are formed by the fertilization of two separate eggs and sperm. Although several nonmammalian animal species can have offspring without fertilization (parthenogenesis), this has not occurred in humans.

Chromosomal errors that occur before or during fertilization can result in formation of an embryo that is haploid, triploid, aneuploid, or containing one or more chromosomes with added or deleted genetic material. Most embryos with serious chromosomal errors die early in development, but some genetic errors cause mild to severe disorders in humans.

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# Exhibit 66

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ORIGINAL ARTICLE

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# Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement

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**Background.** Uterine peristalsis sustains sperm transport and can be detected by hysterosalpingoscintigraphy (HSSG). This study is the first to be designed to investigate utero-tubal transport function by HSSG and uterine contractility by intrauterine pressure measurement (IUP) consecutively on the same day in the periovulatory phase.

**Methods.** Twenty-one female subjects (mean age 28.4 years) without a gynecologic history were examined sequentially by HSSG and IUP on the same day to evaluate uterine contractility in relation to the utero-tubal transport function. In HSSG, intact transport function was visualized by the rapid uptake of <sup>99m</sup>-technetium-marked albumin aggregates through the female genital tract. In IUP, the frequency of uterine contractions (UC/min), amplitude of uterine contractions and basal pressure tone were detected via a intrauterine catheter. HSSG and IUP were embedded in cycle monitoring with measurement of LH and estradiol.

**Results.** In HSSG, a positive transport of inert particles was assessed in 20 of 21 subjects, in 76% to the side of the dominant follicle or on both sides of the oviduct, and in 19% a strict contralateral transport could be observed. In only one subject (5%), no transport was assessed. The mean value of uterine contractions was 3.4 UC/min (SD ± 0.7), the mean amplitude was 12.0 mmHg (SD ± 4.25 mmHg). Basal pressure tone was 70.7 mmHg. There was a statistically significant correlation with estradiol levels: none of the subjects with less than 3 UC/min showed an estradiol level higher than 100 pg/mL; nearly every patient (one exception) with more than 3 UC/min had an estradiol level higher than 100 pg/mL ( $p < 0.0001$ , Fisher's exact test).

**Conclusions.** Intact periovulatory utero-tubal transport function can be documented by HSSG and is caused by directed uterine contractility, measured consecutively by IUP. Uterine contractility is influenced by rising estradiol levels. Directed uterine contractility and intact utero-tubal transport function are considered necessary for intact sperm transport, mainly to the side bearing the dominant follicle to maximize fertility.

**Key words:** intrauterine pressure; intrauterine contractility; HSSG; utero-tubal transport function

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Uterine peristalsis is of critical importance in the process of reproduction and has been investigated mainly by transvaginal ultrasound examination (1,2). Uterine peristalsis only

involves the stratum subvasculare of the myometrium and reveals cyclic changes in direction, frequency and intensity (3,4). During menstruation, contraction waves with the lowest

frequency are directed towards the cervix, while during the other phases of the cycle, with the highest frequency and intensity during the periovulatory phase, cervico-fundal peristalsis prevails (3,5). Uterine contractions are involved in the expulsion of menstrual debris as well as in rapid directed sperm transport (6–9) and in the high fundal implantation of the embryo in the luteal phase.

Two methods have generally been used to assess uterine contractions (UC): one involves a record of changes in intrauterine pressure (IUP) using invasive probes that detect intraluminal variation of pressure produced by the UC (10–12). A less invasive technique has been invented in various forms of direct visualization of UC with transvaginal ultrasound, some from digitized scans. Ultrasound measurements usually provide information on the direction of UC propagation, which is difficult to detect in IUP recordings. In contrast, IUP measurement allows a quantification of the UC amplitude, especially in the periovulatory period.

Hysterosalpingoscintigraphy (HSSG) (13,14) can be used to investigate the utero-tubal transport mechanism of the female genital tract *in vivo* by means of technetium-labeled albumin macro-spheres of the size of sperm that are placed in the posterior vaginal fornix. The ascension of these particles within the female genital tract can be observed by scintigraphy.

In this study, to our knowledge, this is the first time that uterine contractions have been measured in frequency and amplitude by IUP in the late follicular phase, and consecutively correlated with the utero-tubal transport mechanism assessed by HSSG on the same day.

## Material and methods

Twenty-one healthy patients (mean age 28.4 years) with a history of fertility or infertility due to severe andrologic factors were examined by HSSG and measurement of the IUP on the same day in the late follicular phase. All patients had ovulatory cycles and underwent a monitored cycle when HSSG and IUP were performed. Both examinations were undertaken successively on the same day. Ovulation was proven by an LH surge. All patients had proven patency of fallopian tubes by chromolaparoscopy or hysterosalpingosonography.

Exposure of the ovaries to radiation was calculated to be 0.8–1.4 cGy, with the mean exposure below a threshold of 1 cGy. By comparison, radiation exposure in the standard procedure of hysterosalpingography (HSG) is more than seven times higher, at 7.6 cGy.

The study was approved by the local ethics committee and patients gave their informed consent about HSSG and IUP and were strictly advised not to become pregnant during the diagnostic cycle in which HSSG was carried out.

## HSSG

HSSG is a well-established technique for evaluating the utero-tubal transport mechanism (7–9). The examination was performed as close as possible before ovulation in the late follicular phase. On the day of the examination, the size and the location of the dominant follicle were detected ultrasonographically. For HSSG, 10 MBq  $^{99m}\text{Tc}$ -technetium-marked macroalbumin aggregates (Solco MAA; Solco Basel AG, Birsfelden, Switzerland) with a size of 5–20  $\mu\text{m}$ , which imitates the size of sperms, were diluted with 2 mL saline solution 0.9% and then administered in the posterior vaginal fornix of the supine patient. Serial scintigrams were taken by a gamma-camera. For quantitative evaluation of HSSG, 'regions of interest' (ROI) were determined in the area of both fallopian tubes to visualize the concentration of radioactivity in the area of the oviduct. By using ROIs, radioactivity can easily be attached to the compartment's uterine cavity or fallopian tubes. Taking into account the size and location of the dominant follicle, the results of HSSG can be classified as follows:

Ipsilateral: concentration of radioactivity on the side of the dominant follicle.

Contralateral: concentration of radioactivity on the opposite side of the dominant follicle.

Both sides: equal concentration of radioactivity on both sides.

No tubal transport (uterine cavity): concentration of radioactivity in the area of the uterine cavity without any further transport to the fallopian tubes.

## IUP

Each of the 21 women underwent IUP measurement directly after HSSG. IUP was recorded as follows: a rubber balloon-catheter (Ruesch 5 Ch., Ruesch AG<sup>®</sup>, Kernen, Germany) for intrauterine use was gently inserted into the uterine cavity and blocked with 0.5 mL of distilled water. Its hollow cavity was filled with sterile distilled water so that uterine contractions could easily be transferred to a transducer calibrated to convert mechanical to electrical signals. In none of the patients was cervical dilatation necessary, nor was a tenaculum used. Storage of data followed on a PC with specifically designed software (ScopeView, Metex<sup>®</sup>). The exact position of the rubber balloon was estimated in the lower third of the uterine cavity and controlled by transvaginal ultrasound. Recordings lasted 15–20 min.

In every patient the frequency of uterine contractions could be calculated by the number of oscillations per minute and expressed as the number of uterine contractions per minute (UC/min). The amplitude of contractions was expressed in mmHg and defined as the difference from the baseline pressure tone. Basal pressure tone was also detected in mmHg and expresses the basal myometrial activity in the late follicular phase.

In every patient LH and estradiol were measured on the day of the examination.

Documentation of data and statistical analysis was performed with SPSS for windows (SPSS Inc., Chicago, Illinois, USA) on a PC. Statistical significances were calculated with Fisher's exact test. A *p*-value <0.05 was considered to be statistically significant.

## Results

### HSSG

In 16 of 21 (76%) patients an ipsilateral positive transport to the side of the dominant follicle or transport towards both oviducts could be

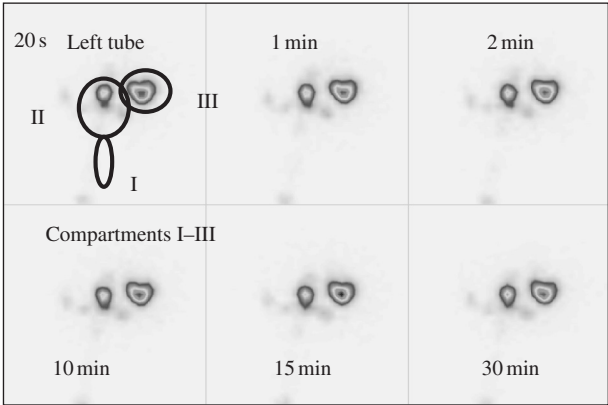


Fig. 1. Hysterosalpingoscintigraphy: demonstration of radioactivity on the left side with a dominant follicle of 15 mm in diameter (ipsilateral demonstration). Compartment I, vagina; compartment II, uterine cavity; compartment III, oviduct. Positive transport mechanism can easily be detected in an early scan after 20 s.

observed (Fig. 1). In four patients (19%) the positive transport could be documented strictly on the contralateral side, in one patient (5%) no tubal transport could be observed (negative transport function). In summary, 20 of the 21 evaluated subjects had a positive transport function of the utero-tubal unit, sustained by uterine contractions. One patient showed a dominant follicle of 17 mm in diameter, an estradiol level of 125 pg/mL, and a contraction of 4.07 UC/min, but failed to build up an intact transport mechanism.

### IUP

In all patients uterine contractions could be easily observed (Fig. 2). The IUP measurement took place in the periovulatory phase directly following HSSG on the same day. Contractions varied between 1.8 and 5 UC/min.

The mean value of contractions in the periovulatory phase was 3.4 UC/min (SD  $\pm 0.7$ ).

The amplitude of contractions varied in range from 8 to 36 mmHg. The mean amplitude was 12.0 mmHg (SD  $\pm 4.25$  mmHg).

The basal pressure tone of the uterus reflects the basal isotonic contraction of this strong muscle containing smooth muscle fibers. In our patients the basal muscle tone was 70.7 mmHg (SD  $\pm 15.7$  mmHg) in the periovulatory phase (Table I).

Depending on the estradiol levels, uterine contractility reveals a statistically significant increase: none of the patients showing less than 3 UC/min had an estradiol level higher than 100 pg/mL (mean 63 pg/mL). By comparison, nearly every patient (one exception) with more than 3 UC/min had an estradiol level higher than 100 pg/mL (mean 201 pg/mL) (Table II,  $p < 0.0001$ ).

### Discussion

Rhythmic contractions of the nonpregnant uterus have been demonstrated by invasive techniques in

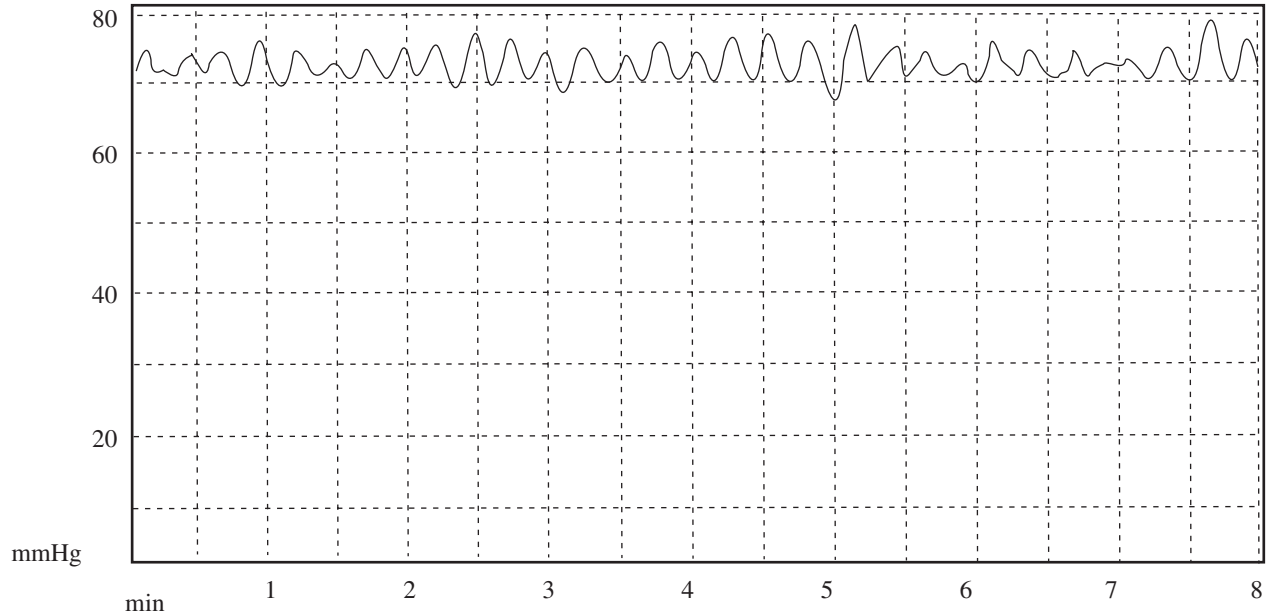


Fig. 2. Contractility pattern demonstrated by IUP in the same patient (see Fig. 1). The patient showed a dominant follicle of 15 mm on the left side, LH peaked on the day of the examination, and the estradiol level was 120 pg/mL. A mean contractility of 3.3 UC/min was detected, with a mean pressure amplitude of 14.1 mmHg and the basal tone was 73.3 mmHg.

Table I. Results from intrauterine pressure measurement ( $n=21$ ) in the periovulatory phase

	Mean	Range
Frequency (UC/min)	3.4 ( $\pm 4.25$ )	1.8-5.0
Amplitude (mmHg)	12.0 ( $\pm 4.25$ )	8.0-36.0
Basal tone (mmHg)	70.7 ( $\pm 15.7$ )	36.0-96.7

different species including humans (10–12). From the end of menstruation until the late proliferative phase most researchers found small and frequent contractions in a retrograde direction (cervico-fundal). The main interest in these first studies was to evaluate uterine contractility during menstruation, which revealed slower and stronger contractions in an antegrade (fundo-cervical) direction.

Before the noninvasive technique of trans-abdominal or transvaginal ultrasonography appeared, the reasons for propagated uterine contractions in the late follicular phase remained enigmatic. Transvaginal studies (3–5) demonstrated a tremendous cyclic increase in frequency and amplitude of uterine contractions towards the fundus uteri throughout the late follicular phase and the periovulatory phase. This contractility pattern was reversed in the luteal phase. The authors presumed that these subendometrial contractions could be of importance concerning sperm transport.

Kunz et al. (8) reported for the first time a direct relationship between the increase in the frequency of uterine contractions assessed by transvaginal ultrasound and the percentage of ipsilateral transport of sperm-like material by HSSG. The mean value for uterine contractions in the preovulatory phase was constantly considered to be in the range 2.8–3.0 UC/min. This process was positively correlated with increasing estradiol levels, but the intrauterine pressure has not been recorded because of its invasive character. Nowadays, HSSG has been established for evaluating the integrity of the utero-tubal transport function (7–9,13,14).

Based upon the encouraging results of these studies, Kadanali et al. (6) reported similar results concerning utero-tubal transport capacity when

radioactive-labeled sperm were used compared to  $99^m$ -technetium-marked albumin macrospheres in patients bearing an intrauterine device (IUD) *in vivo*.

Therefore, there is even *in vivo* substantial evidence that the utero-tubal transport unit is responsible for intact sperm transport.

Contradictory results have also been published (15), although no information was given about the size and location of the dominant follicle and the estradiol levels of the patients examined. The majority of authors working with HSSG support this method as an important diagnostic tool for infertility workup.

To our knowledge, our study is the first to provide proof of an intact sperm transport mechanism assessed by HSSG in healthy women directly followed by IUP measurement. IUP recordings reveal strong and high-frequency contractions that are responsible for the integrity of the utero-tubal transport system.

Although we were not able to investigate the direction of the contraction waves by using only one inserted catheter, the aim of this study was to examine the amplitude, frequency and basal pressure tone in the decisive reproductive phase of the menstrual cycle, results that cannot be obtained by ultrasonographic examination alone.

Uterine contractility at various phases of the menstrual cycle by transvaginal ultrasound and IUP recordings on the same day was first published by Bulletti et al. (16). There was no difference between the measurement of ultrasonographic contractions and contractions measured by IUP recordings, which were 2.9 UC/min in the late follicular phase and 3.9 UC/min in the periovulatory phase. However, IUP recordings were only taken in five subjects.

Our data concerning uterine contractility measured by IUP confirm, in a higher number of subjects, the findings of Bulletti et al., who found a mean value of 3.9 UC/min in the periovulatory phase. Our data revealed 3.4 UC/min at that phase of the cycle. The only difference between the findings is a lower amplitude of uterine contractions (12.0 vs. 25.6 mmHg) and a higher basal tone (70.7 vs. 56.2 mmHg) in our patients. The higher basal tone might be due to the influence of the rubber balloons on the calculated tone pressure.

Failure of an intact utero-tubal transport function as assessed by negative HSSG (no tubal transport) (17) is associated with poor pregnancy rates and might reflect a dissynchronization of uterine wall movements (18).

We found a statistically significant relationship between rising estradiol levels and an increase in UC/min. None of our patients showed less than

Table II. Dependence of uterine contractility on estradiol levels ( $n=21$ )

Frequency (UC/min)	Estradiol	
	<100 pg/mL (mean 63 pg/mL)	>100 pg/mL (mean 201 pg/mL)
<3	8	0
$\geq 3$	1	12



3 UC/min if the estradiol level was higher than 100 pg/mL. This observation indicates that the integrity of utero-tubal transport function transport through the female genital tract is under the endocrine control of the dominant follicle.

As an outlook for further investigations, it would be interesting to perform IUP recordings in patients with endometriosis, as endometriosis and adenomyosis uteri can be regarded as a unique disease – the dislocation of the basal endometrium (19), which is linked with hyper- and dysperistalsis and impeded transport function in HSSG (20). There are data suggesting a higher basal tone of the uterus in patients with endometriosis (21). In patients with endometriosis, a high percentage of structural uterine wall abnormalities are described in transvaginal ultrasonography as well as in T2-weighted magnetic resonance imaging (MRI) (22).

Concerning uterine contractility, patients with endometriosis show a higher frequency, amplitude and basal pressure tone in IUP during menstruation than healthy controls (23). This confirms the results by transvaginal ultrasonography that patients with endometriosis predominantly show a retrograde contractility pattern (in the cervico-fundal direction) (24). These studies might indicate that an increase of cervico-fundal peristalsis might increase the amount of dislocated basal endometrium for intraperitoneal implantation.

Medical treatment studies to reduce uterine contractility are mainly performed in pregnant patients (25,26) but would certainly be of value in reducing dysregulated uterine contractility in patients with endometriosis.

To summarize, our data provide proof that uterine contractility with a mean value of 3.4 UC/min is under the control of the hormonal cycle and regulates the intact uterine transport function assessed by HSSG.

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# Exhibit 67

## The Transport of Carbon Particles in the Human Female Reproductive Tract

G. E. Egli, M.D., and Michael Newton, M.D.

**T**HE METHOD by which spermatozoa reach the oviduct remains an important problem in mammalian reproduction. Since spermatozoa possess motility, it has been widely assumed to be the most important factor. However, work in cows suggests that it may not be the chief means of transport. Thus, Vandemark and Moeller recovered spermatozoa from the oviduct 2½ min. after mating. This is far sooner than could be expected on the basis of the inherent motility and sense of direction of spermatozoa.

Work in animals indicates that muscular contractions of the reproductive tract may aid in the transport of spermatozoa and that the oxytocic hormone may play a part in this process. Vandemark and Hays<sup>11</sup> noted that a crescendo of uterine contractions took place before and during copulation in the cow. Furthermore, stimulation of the cow's genitalia produced a rise in intramammary pressure.<sup>7</sup> Normally such a change is brought about by the release of oxytocin from the posterior pituitary gland during the letdown or ejection reflex as the calf or milking machine is applied to the teat.<sup>5</sup> Finally, in-vitro studies by Vandemark and Hays<sup>12</sup> demonstrated that when oxytocin was added to the solution perfusing the isolated cow's uterus, the rate of transport of spermatozoa was increased.

Evidence that the same process occurs in humans is scanty. Because of the difficulty of using spermatozoa, inert particles have occasionally been employed experimentally. Amersbach placed a cap containing a suspension of carbon particles over the cervix. Following coitus he was able to recover

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particles from the cervical canal. Trapl had a patient insert carmine particles into the vagina immediately after intercourse. Twenty-four hr. later at laparotomy he found numerous particles in the uterine tubes. Furthermore, it has been suggested that there may be a sucking effect as a result of uterine contractions occurring at orgasm that pulls semen through the cervix into the uterus.<sup>8</sup> There is also some evidence that oxytocin is released at the time of orgasm in humans.<sup>4,9</sup> However, the time relationships and precise mechanisms of transport of inert particles or spermatozoa have not been elucidated in humans. The paucity of information in this regard has been pointed out by Hartman in his excellent review article.

If human spermatozoa move at a rate of 3 mm./min.,<sup>3</sup> it should take a spermatozoon, moving on a direct course, at least 45 min., in the average woman, to travel from the cervix to the junction of the middle and outer thirds of the tube, where fertilization occurs. If the action of the uterine or other muscles of the reproductive tract is important in humans, then not only spermatozoa but also inert particles should reach the tube much sooner than this. The present study was designed to determine whether, under reasonably controlled conditions, carbon particles could be transported quickly from the vagina to the tubes.

## METHODS

It seemed desirable to set up, as far as possible, conditions that were optimal for rapid transport. Thus, patients were selected who required an elective abdominal hysterectomy that could be scheduled at or near the day of ovulation. They had to be of reproductive age, to have proved fertility, and to have relatively normal reproductive organs. A suspension of carbon particles in Dextran was made up so that the particles were similar in size to spermatozoa and that the solution was of the consistency of seminal fluid. This was done by mixing 30% Dextran with 4% bone black. In addition, it was decided to use intramuscular oxytocin to aid in the transport of the particles, because of the experimental evidence indicating its possible importance.

Three women fulfilling the above criteria were studied. In each instance the procedure was as follows: Soon after general anesthesia had been induced, the patient was placed in the lithotomy position with her head tilted downward at an angle of 15° from the horizontal. A speculum was introduced into the vagina, and 3–4 ml. of sterile carbon particles–Dextran suspension were deposited in the posterior fornix. At the same time 1 ml.

(10 U.) of oxytocin was given intramuscularly. The speculum was removed, and the patient was immediately returned to the supine flat position. Her abdomen was promptly opened, and before the uterus was manipulated, a suture was placed tightly around the tubes about 1 cm. lateral to the uterus. The tubes were excised and taken to the laboratory, where they were flushed with saline from the infundibular portion downward. The solution was collected on clean slides and examined under the microscope for carbon particles.

## RESULTS

The first patient was 32 yr. of age, gravida 6, para 6, and was at the fourteenth day of her cycle, which was usually about 28 days in length. Twenty-eight min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. Many carbon particles were found in the washings from both tubes. On microscopic examination the endometrium was described as being early progestational.

The second patient was 30 yr. of age, gravida 6, para 6, and was at the twelfth day of her cycle, which was usually about 28 days in length. Thirty-four min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. Carbon particles were recovered from both tubes. On microscopic examination the endometrium was described as being estrogenic.

The third patient was 41 yr. of age, gravida 8, para 7, aborta 1, and was at the thirteenth day of her cycle, which was usually about 28 days in length. She was a diabetic and had aborted three mo. previously. Twenty min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. No carbon particles were found in the washings from either tube. On microscopic examination the endometrium was described as being early progestational.

## DISCUSSION

This study indicates that in two cases, under the conditions outlined, inert carbon particles, placed in the posterior fornix of the vagina, were found 28 and 34 min. later in both tubes. How they reached the tubes is a difficult question to answer. Certainly they did not proceed by their own movements. It is reasonable to suppose that some sort of movement of the uterus and/or tubes contributed to the transport of the particles.

Movements of the reproductive organs and particularly the uterus could be due to inherent motility, general body movements, the effect of anes-

thesia, or the influence of the injected oxytocin. The uterus undoubtedly possesses inherent motility. Conceivably this could be sufficient to aid the transport of particles into the tubes, although it might well have been decreased by the anesthesia used. Bodily movements were held to a minimum. The patients were on their backs at all times, and so virtually no opportunity for the suspension to enter the uterus or tubes by gravity was afforded. Manipulation consisted only of removing the speculum, returning the patient to the supine position, opening the abdomen, and ligating the tubes. The effect of anesthesia would be, in general, to reduce uterine motility: However, spasm of the cervix or uterotubal opening could have been relaxed by the anesthesia. The theory that oxytocin does contribute to the transport of particles is most attractive, but at the present time we have no proof of it. Further in-vivo and in-vitro experiments are being done in pursuit of a solution to this problem.

The fact that in one case transport of carbon particles to the tubes was not demonstrated is not surprising. One of several factors may have contributed to this. Possibly the hormonal conditions present in the uterus were not optimal.<sup>2</sup> The patient's recent abortion may have been important. Finally, it is conceivable that insufficient time was allowed for transport.

### SUMMARY AND CONCLUSIONS

Carbon particles, suspended in 30% Dextran, were placed in the vagina in three anesthetized women who were about to undergo elective abdominal hysterectomy at about the time of ovulation. At the same time oxytocin was injected intramuscularly. In two of the three women carbon particles were recovered from the tubes 28 and 34 min. later.

These data, together with other work in animals and humans, support the belief that the motility of spermatozoa is not the chief factor in sperm transport. Contractions of the muscle of the uterus or other reproductive organs may be very important, and it is possible that oxytocin may play a part in this process.

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# Exhibit 68

high. The few cases in which progestin therapy resulted in improvement of symptoms and relief of obstruction suggest that there may be a place for selective medical management. Patients who are young and wish to preserve their childbearing capacity may be considered initially for such treatment. Fertility potential is probably poor in this group of patients because of the extent of their pelvic endometriosis. Patients considered for medical management should be informed of the risks of permanent renal damage and treated with close surveillance of renal function.

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## RETROGRADE MENSTRUATION IN WOMEN UNDERGOING CHRONIC PERITONEAL DIALYSIS

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Blood in the peritoneal dialysis catheter just before menstruation was regularly observed in 9 of 11 premenopausal women maintained on peritoneal dialysis for end-stage renal failure. Peritoneal bleeding at other times during the menstrual cycle was not seen in any of these patients. Likewise, peritoneal bleeding in men or nonmenstruating women on chronic peritoneal dialysis was exceedingly rare, was not periodic, and usually was due to recognizable causes. These observations suggest that retrograde menstrual bleeding into the peritoneal cavity is the rule rather than the exception in women on peritoneal dialysis and possibly in all menstruating women. Implications of this observation for the pathogenesis of endometriosis and dysmenorrhea are discussed. (*Obstet Gynecol* 57:667, 1981)

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The incidence of retrograde menstruation and its consequences have been the topic of extensive debate. Sampson<sup>1</sup> suggested that retrograde menstruation is the cause of external endometriosis, noting that blood was frequently observed escaping from the ostia of the fallopian tubes in menstruating women who were undergoing pelvic surgery. Novak questioned this theory on the grounds that retrograde menstruation was rare as compared to the observed frequency of endometriosis.<sup>2,3</sup> Watkins reported bloody fluid containing endometrial cells aspirating from the cul-de-sac during menstruation.<sup>4</sup> Other reports note the occasional appearance of blood in the pelvic cavity at the time of culdoscopy or pelvic surgery when performed during menstruation.<sup>5-9</sup>

This communication describes observations in menstruating women on maintenance peritoneal dialysis who were noted to have blood in the peritoneal catheters or in the effluent dialysate coincident with menstruation.

## Patients and Materials

The development of implantable Silastic catheters has made it possible to maintain selected patients with end-stage renal failure alive and well for extended periods by means of peritoneal dialysis.<sup>10</sup> A silicone rubber catheter is implanted through the abdominal wall with its intraabdominal section usually lying in the pelvic cavity. During intermittent peritoneal dialysis,

sterile dialysate is pumped through the catheter into the peritoneal cavity, where it remains for a specified dwell period; then it is drained and replaced by fresh dialysate. This cycle is generally repeated every 30 minutes during a 12-hour overnight treatment period. Most patients require 3 treatments per week. The transparent external catheter segment is closed between treatments by a disposable rubber cap and represents a fluid-filled extension of the peritoneal cavity. The character of the peritoneal fluid in the catheter can be observed prior to dialysis or in the effluent of the initial dialysis cycle. Heparin was not routinely added to the dialysate in any of these patients. Bleeding into the peritoneal cavity is usually readily detectable by the presence of a red thread of sedimented red blood cells within the transparent external Silastic catheter segment. Occasionally blood is not apparent until the first exchange of dialysate is being drained.

The records of all women between the ages of 15 and 50 who were maintained on peritoneal dialysis were reviewed. A total of 11 women with a history of menstrual bleeding after initiation of maintenance peritoneal dialysis was identified (Table 1). All patients were interviewed to obtain a detailed menstrual history to supplement the official record. At the time of data collection 5 of the women were no longer on peritoneal dialysis; 3 had undergone successful renal transplantation and 2 had been switched to hemodialysis. At the time of the interview, patients 10 and 11 had only a vague recollection of their menstrual history.

The 11 patients had a mean age of 38.8 years (range, 15 to 44 years); all had been on maintenance home peritoneal dialysis and were followed at the University

of Washington or the Northwest Kidney Center in Seattle. Uremic symptomatology was controlled in all these patients and they were as well as comparable patients undergoing hemodialysis. Eight of the 11 women had experienced cessation of menstruation prior to dialysis; 1 patient had primary amenorrhea, 4 were nulliparous, and 7 were multiparous.

Three of the 11 women who were on maintenance peritoneal dialysis at the time of the survey had peritoneal fluid collected on several occasions in the course of their menstrual cycles and when blood was in evidence. The fluid specimens were aspirated aseptically from the peritoneal catheter and placed into sterile glass flasks, which were sent immediately or after overnight refrigeration to the cytology laboratory for processing.

### Results

Eight of 11 women listed in Table 1 developed secondary amenorrhea coincident with the development of chronic renal failure. All 8 resumed menstruation after maintenance peritoneal dialysis was instituted. The mean time interval from the beginning of dialysis to resumption of menstruation was 7.7 months. Menstruation had not ceased in patients 6 and 11. Patient 7 had primary amenorrhea. Of the 9 patients who experienced resumption of menstruation or menarche after initiation of peritoneal dialysis, 5 were noted to have regular menses and 6 had irregular menses. With the exception of patients 10 and 11, both of whom had only 2 very scanty periods, all patients were noted to have small amounts of blood in their peritoneal catheter and/or in the effluent dialysate coincident with

**Table 1.** Menstrual History of Women Who Had Noted Blood in Catheter and/or Effluent Dialysate While Undergoing Maintenance Peritoneal Dialysis

Patient	Age at onset of dialysis	Cessation of menstruation prior to dialysis	Months of dialysis until resumption of menstruation	Menstruation		Blood in catheter and/or effluent dialysate
				Regularity	Flow	
1	17	Yes	3	Regular	Moderate	Yes
2	21	Yes	6	Regular	Moderate	Yes
3	40	Yes*	5	Irregular	Heavy	Yes
4	40	Yes	5	Irregular	Scanty	Yes
5	36	Yes	12	Regular	Moderate	Yes
6	34	No	—	Irregular	Moderate	Yes
7	15	—†	32	Regular	Scanty	Yes
8	44	Yes	2	Regular	Moderate	Yes
9	25	Yes	3	Irregular	Heavy	Yes
10	40	Yes	—	Irregular	Scanty‡	No
11	27	No	—	Irregular	Scanty‡	No

\* Contraceptive injection.

† Primary amenorrhea.

‡ Only 2 periods.



the time of menstruation. Blood always appeared in the dialysate or in the catheter a few days prior to the onset of vaginal bleeding, and it usually persisted during the first day of menstrual flow. Patient 6 consistently noted blood in the peritoneal catheter 4 days before the onset of menstruation. In several of the patients the appearance of blood in the dialysate was the first sign of the return of menses after secondary amenorrhea. In patient 7, menarche was noted at the age of 19 by the appearance of peritoneal blood. This patient had started dialysis at the age of 15, at which time she had no secondary sexual development.

Six of the 11 patients (patients 1 through 5 and 7) eventually underwent laparotomy for nephrectomy and/or splenectomy prior to renal transplantation. In none of these patients was endometriosis noted at the time of abdominal surgery. Menstrual blood loss did not have a significant effect on hematocrit levels in these women, none of whom required blood transfusions once stabilized on peritoneal dialysis. Although numerous attempts were made in 3 of the patients to identify endometrial or tubular epithelial cells in the peritoneal effluent or aspirate, unequivocal evidence for such cells in any of the specimens was not obtained.

### *Discussion*

With advancing renal failure, as with other debilitating diseases, secondary amenorrhea often develops. Hemodialysis therapy has been reported to be associated with resumption of menstrual periods in some patients, menorrhagia in others, and persistent amenorrhea in a third group.<sup>11,12</sup>

In this series 11 women under the age of 45 who were treated with chronic peritoneal dialysis and who continued or resumed menstrual periods are reported. The presence of an implanted intraabdominal catheter afforded an opportunity to observe the character of peritoneal fluid over months or years. When patient 1 first noted blood in the effluent dialysate she was alarmed, and her physician was at a loss to explain the phenomenon. This first episode was not associated with vaginal bleeding. In subsequent months, blood staining of her peritoneal fluid occurred at regular intervals in association with vaginal bleeding. In the course of subsequent years the same phenomenon was observed in all women who resumed menstrual cycles while undergoing peritoneal dialysis. The 2 exceptions were patients 10 and 11, each of whom had only 2 periods with very scanty flow after initiation of dialysis. As both had undergone dialysis at home and neither was a good observer, it is conceivable that small amounts of peritoneal blood may have escaped their

attention. Resumption of periods was often indicated by blood in the effluent dialysate before vaginal bleeding occurred.<sup>13</sup> None of the women had a history of dysmenorrhea or showed evidence suggestive of pelvic endometriosis; this was verified in 6 of the 11 women during pretransplant laparotomy. In men and nonmenstruating women, blood in the peritoneal catheter or effluent dialysis is exceedingly rare and usually can be explained by a detectable anomaly such as peritonitis, intraabdominal malignancy, recent abdominal surgery, or tissue herniation into the implanted catheter with subsequent hemorrhage.

The authors think it highly unlikely that hormonal alterations or anatomic abnormalities associated with chronic renal failure or dialysis explain the high frequency and regular occurrence of blood in the peritoneal cavity coincident with the time of menstruation. Likewise, it would appear most unusual for mechanical irritation by the peritoneal catheter to occur exclusively in menstruating women and in association with menstrual flow. These observations suggest strongly that retrograde bleeding regularly occurs with menstruation in most if not all women on peritoneal dialysis and quite possibly in most menstruating women in the general population.

The current emphasis on prostaglandin as a possible cause of dysmenorrhea notwithstanding,<sup>14</sup> it remains intriguing to speculate on the role that retrograde menstruation may play in the pathogenesis of dysmenorrhea. If retrograde menstrual bleeding is the rule rather than the exception, then bleeding must be asymptomatic in most women as it was in these patients, none of whom has a history of dysmenorrhea. As most women do not experience dysmenorrhea, this lack of pain may be a reflection of low peritoneal reactivity to irritation by blood or other irritants. Variability in the pain threshold to intraabdominal blood is well known to surgeons confronted with hemo-peritoneum and to gynecologists treating endometrial disease. Similarly, the present authors and others with extensive peritoneal dialysis experience have observed remarkable individual differences in abdominal pain response to acid peritoneal dialysis solutions. Thus, both the amount of blood spill and individual reactivity may be important modulating factors in the causation of dysmenorrhea. In this context, it may also be of interest to recall that retrograde bleeding usually occurred 1 or several days prior to the onset of vaginal bleeding and ceased when vaginal flow commenced, a pattern analogous to that of the pain prevalent in dysmenorrhea, especially in nulliparous women.

Cervical or other obstruction to free flow during the initial phase of menstruation may contribute to or aggravate abdominal spillage of blood and may help ex-

plain premenstrual pelvic congestion and its relief by establishment of cervical blood flow, especially in nulliparous women. Obstruction to free flow also appears to be associated with early establishment of pelvic endometriosis in teenagers,<sup>15,16</sup> an age group not normally affected by this disease.

The observation of frequent, perhaps regular retrograde menstruation in most women tends to support Sampson's theory of retrograde menstrual bleeding as the most likely and most frequent cause of pelvic endometriosis. Watkins<sup>9</sup> had rejected this notion because he believed retrograde bleeding was too infrequent to account for the incidence of endometriosis. However, it was Watkins who reported endometrial cells in the cul-de-sac of menstruating women, a finding supported by other workers in this field, most recently by Gahl,<sup>17</sup> who observed tubal epithelial cells in the peritoneal effluent of women undergoing peritoneal dialysis. Although retrograde bleeding does not explain why only some women develop endometriosis, these findings rebuke Watkins' objections to the spill-implantation theory of endometriosis.

### Addendum

Since the compilation of the data for this report, the authors have treated additional patients who menstruated while being maintained on peritoneal dialysis. All showed evidence of retrograde bleeding in the catheters or in the initial peritoneal effluent, except 1 patient who had undergone tubal ligation.

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## FATAL CASE OF CYTOMEGALOVIRUS PNEUMONITIS IN A POSTPARTUM WOMAN

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This is the first reported fatal case of cytomegalic inclusion disease in a pregnant woman. The 28-year-old woman died after cesarean section for cephalopelvic disproportion. The diagnosis of cytomegalic inclusion disease was made at autopsy by finding enlarged pneumocytes with typical intranuclear inclusions, positive direct immunofluorescence on the lung tissue with antibody specific for cytomegalovirus, and retrospective serologic titers of 1:64 for the virus. The time of the infection is unclear, but the absence of infection in the newborn may suggest an onset late in pregnancy; there was no evidence of disease before labor and cesarean section. (*Obstet Gynecol* 57:670, 1981)